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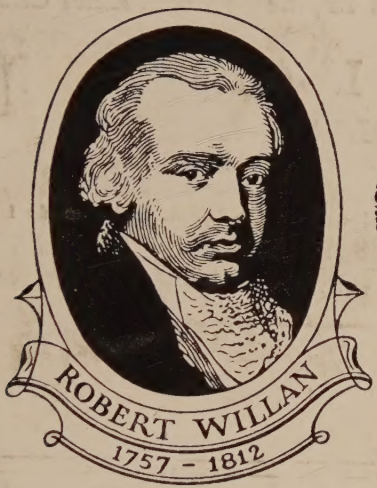

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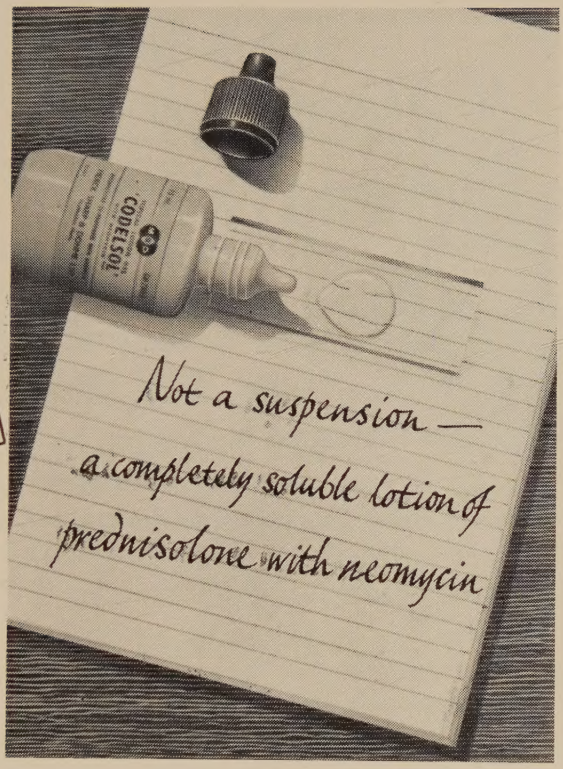

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OCTOBER 1958

INVESTIGATIONS INTO CANTHARIDIN BLISTERS RAISED ON APPARENTLY NORMAL SKIN IN NORMAL AND ABNORMAL SUBJECTS.

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AND
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THE cantharides blister and its contents have already been studied extensively and from various aspects. Miescher (1936) drew attention to the striking early acantholysis that occurs and is followed by exudation into the epidermal fissures thus formed. The studies of Ewald (1939) and of Samter (1948) were concerned mainly with the cell content of the blisters which, in the present investigation, we have not considered in any detail. Pezold and Hinz (1953) have made comparisons between the protein content of the plasma, of the blister fluid, and of the " tissue fluid " which can be obtained by suction from the floor of a recently-opened blister.

Bonelli and Datovo (1957) compared the protein content of plasma with that of blister fluid in a variety of dermatoses, mainly bullous diseases. They examined fluid from the natural blisters of the disease and also blisters produced with cantharides. They found that the relative protein fractions in the blister fluid corresponded closely with those in the plasma ; the relation between the total protein content of blister fluid and of plasma was however very variable.

The aim of this work has been to compare the response of the normal skin of normal and eczematous subjects to applications of cantharidin. In addition it was found helpful to compare these responses with those obtained in patients whose vascular response was known to be abnormal.

Material.

Preliminary studies of patients with less than 10–15% of the skin affected by eczema other than atopic eczema did not show results outside the normal range.

In view of this all the non-atopic eczematous subjects chosen had eczema that involved more than this proportion of their skin surface, or had been so affected within the preceding four weeks. This group consisted of seborrhoeic eczema, seven cases (12),* disseminated hypostatic eczema, six cases (10), and nummular eczema, eight cases (13).

The atopic patients were divided into those with habitually more, seven cases (16), and those with invariably less than about 15% of skin involvement, six cases (7).

The urticaria group was studied because this type of case appears to have an abnormality of vascular response leading to increased capillary permeability. The group included five cases (7) of giant urticaria, five (5) of factitious urticaria and one (1) of athrombocytopenic purpura.

No patient with asthma, allergic rhinitis or a past history of eczema was included in the control group of fourteen subjects (15).

The control group, the atopic group and the urticaria group were strictly comparable as to age and sex. The subjects in the other eczema groups were somewhat older than the control series.

The test subjects were not under the influence of any systemic treatment at the time of testing, except when oral prednisone was given, either as an essential part of treatment or in order to study its effect. Apart from this Seconal $1\frac{1}{2}$ grains was allowed on the night of the test if the patient was in the habit of taking a sedative.

Method.

Blisters were raised on areas of normal skin by applying a disc of cantharidin 0·2% in a base of Lead Plaster Mass B.P.C. 1934 on canvas backing. The discs measured 22 mm. in diameter. A plastic ring protected the test area from trauma. The site tested was either the front of the abdomen or the front of the mid-forearm. Twenty hours later the application was removed, and the blister lid opened with scissors. The fluid was drained into a perspex cup, and transferred to a glass tube containing one drop of heparin (5000 i.u. per ml.).

The volume of fluid with its total white cell count and total protein concentration were measured.

At the end of the test a sample of venous blood was taken and the total plasma protein concentration, white blood cell count, and erythrocyte sedimentation rate (Wintrobe) were determined (Wintrobe and Landsberg, 1935).

* Figures in brackets refer to number of tests.

The total protein estimations in the blister fluid and plasma were made by the Biuret technique (Gornall *et al.*, 1949).

Results.

Blister Volume.

Both atopic groups gave blister volume figures significantly higher than normal.

In no other group was the blister volume outside the normal range (Table I).

Table I.—*Blister Volumes.*

Group.	Number of tests.	Mean volume in ml.	Standard Deviation.	P^*
Atopics (<15% of skin affected)	7	1·41	0·5	<0·001
Atopics (>15% of skin affected)	11	1·90	1·09	<0·001
Seborrhoeic (>15% of skin affected)	11	0·62	0·30	—
Hypostatic (>15% of skin affected)	10	0·84	0·30	—
Nummular (>15% of skin affected)	13	0·80	0·40	—
Urticaria Group	13	0·71	0·31	—
Normals	14	0·67	0·33	—

P^* = The probability of the difference between each group and the normal group being due to chance.

The blister volumes in widespread atopic dermatitis were significantly higher than the blister volumes in the other eczema groups (Table II).

Table II.—*Blister Volumes.*

Group.	Number of tests.	Mean volume in ml.	Standard Deviation.	P^*
Atopics (>15% of skin affected)	11	1·9	1·09	<0·001
Seborrhoeic (>15% of skin affected)	34	0·762	0·34	—
Hypostatic (>15% of skin affected)				
Nummular (>15% of skin affected)				

P^* = The probability of the difference between the two groups being due to chance.

The blister volume in patients with atopic eczema sometimes could not be measured owing to leakage from the blisters before aspiration was due. This was possibly because the blisters were larger. When prednisone was given, large intact blisters were obtained and the blister roof appeared to be stronger, so that those receiving prednisone appeared to have larger blister volumes. The possibility that prednisone actually increased the fluid output was disproved, because when intact blisters were available for comparison, no change could be detected in the volume of blister fluid before and after giving prednisone.

Blister Proteins.

As the blister protein concentration might possibly be related to the circulating plasma protein concentration, the blister protein was expressed as a ratio of the plasma protein, thus obtaining a " B/P ratio ".

$$\text{" B/P ratio "} = \frac{\text{Blister fluid protein concentration g/100 ml.}}{\text{Plasma protein concentration g/100 ml.}}$$

When comparing the B/P ratio in the various groups, the atopic group was again shown to give results furthest from normal, the figures obtained in the other groups of eczema holding an intermediate position between the normals and atopics (Table III).

The urticaria group gave figures within the normal range.

TABLE III.—*B/P Ratios.*

Group.	Number of tests.	Mean B/P ratio.	Standard Deviation.	P*
Atopics (<15% of skin affected)	7	0·741	0·033	<0·02
Atopics (>15% of skin affected)	16	0·790	0·035	<0·001
Seborrhoeic (>15% of skin affected)	12	0·739	0·031	<0·01
Hypostatic (>15% of skin affected)	10	0·743	0·047	<0·01
Nummular (>15% of skin affected)	13	0·748	0·040	<0·01
Urticaria Group	13	0·692	0·034	—
Normals	15	0·687	0·049	—

P* = The probability of the difference between each group and the normal group being due to chance.

The B/P ratio in the group with widespread atopic eczema was significantly higher than in the other eczema groups with comparable degrees of skin involvement (Table IV).

TABLE IV.—*B/P Ratios.*

Group.	Number of tests.	Mean B/P ratio.	Standard Deviation.	P*
Atopics (>15% of skin affected)	16	0·790	0·35	<0·001
Seborrhoeic, Hypostatic, Nummular (>15% of skin affected)	35	0·744	0·038	—

P* = The probability of the difference between the two groups being due to chance.

The higher B/P ratios found in the atopic and the eczema groups as compared with normals could be due to a relatively higher blister protein or to a relatively lower plasma protein or to both.

The plasma and blister protein concentrations which went to form the B/P ratios were analysed to elucidate this point, and are shown in Tables V and VI.

TABLE V.—*Blister Protein Concentration.*

Group.	Number of tests.	Mean blister protein (g. %).	Standard Deviation.	P^*
Atopics (>15% of skin affected)	16	5·70	0·32	<0·001
Seborrhoeic, Hypostatic, Nummular (>15% of skin affected)	35	4·97	0·32	—
Normals	15	4·82	0·45	—

P^* = The probability of difference between the blister protein concentrations and normal being due to chance.

TABLE VI.—*Plasma Protein Concentration.*

Group.	Number of tests.	Mean plasma protein (g. %).	Standard Deviation.	P^*
Atopics (>15% of skin affected)	16	7·22	0·34	—
Seborrhoeic, Hypostatic, Nummular (>15% of skin affected)	35	6·68	0·26	<0·01
Normals	15	7·02	0·47	—

P^* = The probability of difference between the plasma protein concentrations and normal being due to chance.

From this it will be seen that in atopics the higher B/P ratio was due to a rise in the blister protein concentration relative to the blister protein concentration in the normal group.

In the other eczemas the blister protein concentrations were not significantly above normal, and the raised ratio was almost entirely produced by a lower plasma protein concentration than normal.

Histology of Blister Roofs.

The general histological changes that follow an application of cantharides have been described by Miescher (1936). It should be noted that the type of skin damage differs from that in eczema, and these experiments do not in any sense reproduce the lesions of the disease.

We have examined the blister roofs of 11 eczematous and 11 non-eczematous patients. The only difference found was a relatively larger number of a particular type of acantholytic cell in the eczematous patients. These cells had a pyknotic nucleus surrounded by a clear zone separating it from the cell cytoplasm (Fig. 1). These changes were most evident in tissue removed from patients with atopic as opposed to other forms of eczema.

A satisfactory means of expressing these differences quantitatively was not

found. Treatment with oral prednisone did not appear to influence these changes.

Erythrocyte Sedimentation Rate (Wintrobe) (ESR).

Patients with hypostatic eczema and secondary spread had ESRs slightly above the normal range. This was so for the crude sedimentation rate and for the rate compensated to a Packed Cell Volume of 45% (Table VII).

No other groups showed sedimentation rates above normal.

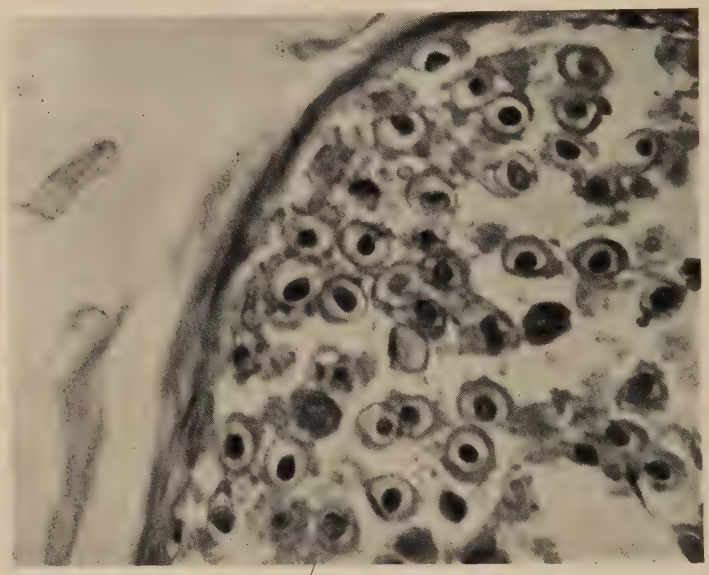

FIG. 1.—Cantharides blister lid removed from a case of atopic eczema at twenty hours.

TABLE VII.—*ESRs of Normals and Hypostatic Eczemas Compared.*

Group.	Mean ESR compensated to PCV 45%.	Standard Deviation.	*P**	Mean actual ESR	Standard Deviation.	*P**
Hypostatic eczema	27	8	<0·02	36	9·4	<0·01
Normals	14·5	12·1	—	15·9	14·3	—

*P** = The probability of the difference between the sedimentation rates in hypostatic eczema and normals being due to chance.

Peripheral White Blood Cell Count.

The blood leucocyte count was higher in cases of widespread atopic eczema than in normals (Table VIII).

The other groups had counts within the normal range.

TABLE VIII.—*Peripheral White Blood Cell Count.*

Group.	Number of tests.	Mean total WBC count.	Standard Deviation.	P^*
Atopics (<15% of skin affected)	7	7914·3	2472	—
Atopics (>15% of skin affected)	12	9314·3	2624	<0·001
Normals	8	6650	1975	—

P^* = The probability of the difference between the leucocyte counts in the atopic groups and normals being due to chance.

Blister Fluid Leucocyte Count.

The only group with blister fluid white cell counts outside the normal range were those atopic subjects with less than 15% of the skin surface involved; their counts were significantly lower than normal. In this connection it must be remembered that in the two atopic groups there was a much greater dilution factor (Table IX).

TABLE IX.—*Blister Fluid Leucocyte Count.*

Group.	Number of tests.	Mean WBC.	Standard Deviation.	P^*
Atopics (<15% of skin affected)	6	825·0	451	<0·001
Atopics (>15% of skin affected)	12	2776·7	2729·5	—
Normals	8	2144	1256	—

P^* = The probability of the difference between the atopic groups and the normals being due to chance.

DISCUSSION.

The main results may therefore be summarized :— First, the volume of blister fluid formed is greater in the atopic group and normal in the other groups tested.

Second, the protein concentration in the blister relative to that of the plasma is greatest in atopic subjects and greater than normal in the other eczema groups.

The histological studies of Miescher (1936) have indicated that it is on the epidermis that cantharides exerts its initial effect; acantholysis is already well developed before any marked vascular reaction can be seen. The vascular dilatation and exudation that follow may be due to some substance liberated from the damaged epidermis, or may be produced by cantharidin itself which has penetrated the acantholytic epithelium to act directly on the vessel wall. In either case the degree of vascular exudate will largely depend upon the amount of epidermal damage.

Previous workers, e.g. Bonelli and Datovo (1957), have apparently assumed that the blister protein originates exclusively from the capillaries and therefore depends upon their degree of permeability. It seems, however, that damaged

epidermal cells may also contribute to the blister protein and may indeed be a factor that greatly influences the B/P ratio. Since this, and the degree of vascular exudate both depend upon epidermal damage, we conclude that the B/P ratio may be taken as an index of epidermal damage.

If the blister protein has come mainly from the capillaries, then cantharidin must have produced a greater degree of vascular permeability in atopic and eczematous subjects than in normals. The fact that the urticaria group results were normal although vascular permeability is likely to be more easily produced in that group, suggests that the increased permeability in eczema and atopy is due to the action of the cantharidin on the vessels being modified by an altered epidermis.

If, on the other hand, a considerable proportion of the blister fluid protein has arisen from damaged epidermal structures, then the results in eczema and atopy again indicate an abnormality in the epidermis.

Our limited histological studies seem to indicate some difference in the degree of acantholysis in the eczema and atopic groups as compared with the controls.

For these reasons we conclude that in the atopic and eczema groups the epidermis of apparently normal skin is more readily damaged by cantharidin than the skin of a normal person. This fragility is very much greater in subjects with atopic eczema than in those suffering from seborrhoeic nummular of widespread hypostatic eczema.

Summary.

The results of applying cantharidin 0·2% for 20 hours to the normal skin of eczematous subjects and patients with known increased capillary permeability are presented and the results compared with controls.

1. Patients with atopic eczema produce larger blisters containing more protein both absolutely and relative to their own plasma than do normals or other types of eczema of comparable severity.

2. Patients with seborrhoeic, hypostatic and nummular eczema produce blisters of normal size containing more protein relative to their plasma than do normals.

3. Patients with urticaria produce blisters of normal size, absolute protein content, and protein content relative to their own plasma.

4. The blister lids removed from subjects with atopic eczema 20 hours after the application of cantharidin showed many acantholytic cells of a type infrequently seen in the lids from non-eczematous subjects.

5. Patients with more than 15% of their skin affected by atopic eczema had a significantly raised peripheral white blood cell count.

6. Patients with less than 15% of their skin affected by atopic eczema had

a significantly lower blister fluid white cell count than the other groups tested. This was related to the excessive volume of blister fluid formation.

The implications of these results are discussed.

We are very grateful to the following for their help : Dr. R. H. Meara, Dr. C. D. Calnan, and Mr. L. P. Le Quesne for permission to investigate cases under their care ; to Dr. Drew Thomson for his assessment of the histological findings ; to Dr. H. Lloyd and Mr. N. F. Robinson for their help with the haematological studies ; to Mr. C. F M. Rose for his advice on biochemical matters, and to Mrs. A. J. Foster for the statistical studies.

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NECROBIOSIS LIPOIDICA

A. NANTA, A. BAZEX, AND A. DUPRÉ.

Toulouse, France.

THIS report may appear at first sight contradictory and negative ; contradictory because two cases presented a histology which was the reverse of their clinical appearance and negative because these findings seem to deny the specificity of the histological picture of N.L. These cases evidently require different interpretation and although the histological picture is not of the classical type they must nevertheless be included in the category of N.L. If histochemistry in its present state of development does not allow us to separate two or three different conditions it is perhaps because it is not sufficiently developed ; or better still because the answer does not lie with histochemistry but with a more subtle histogenesis.

Our investigations comprise 13 different cases under observation at the present time to which we may add four previous cases of which the first was published by two of us in 1938 as the first French case (Nanta and Bazex, 1938). The 13 present cases include three of necrobiosis lipoidica diabeticorum, five of N.L. without diabetes, and five of granuloma annulare with lipoid imbibition. This classification of cases which are aetiologically and morphologically related but distinct one from the other, has already been studied from a variety of aspects and presents no serious outstanding problem. On the other hand, two of these cases require our attention because they present peculiarities which are remarkable if not entirely new.

The first case, hitherto unpublished, is one of xanthomatosis in a young man, developing in the manner of an eruptive xanthoma and with the morphology and localisation of that disorder, but in which histological examination showed the structure of typical N.L. So great was this resemblance that one must wonder whether the two disorders do not have the same nosological significance.

The second case was the other way round, that of a diabetic with the clinical diagnosis of N.L. of the type resembling erythema elevatum diutinum. Clinically the diagnosis of lipoidosis was inadmissible but the histological structure was nevertheless that of a lipoidosis. These cases prompt the following observations.

1. Caro Paton (1952) and then Baccaredda (1955) expressed the opinion formerly expressed in France that erythema elevatum diutinum is related to granuloma annulare. They report cases in which the histology does not show the presence of lipoid in the tissues. May it not be then that two disorders

which are clinically different may present in the first place in a stage before lipoid infiltration has begun.

2. In regard to lipoid infiltration of E.E.D. Degos *et al.* (1952) describe a case in which the histology showed a granulomatous infiltration without necrosis but with an abundant infiltration of histiocytes containing lipoid. Laymon (1937), Weidman (1943), and Cortello (1947) have discussed this lipoid infiltration at some length.

3. More recently Herzberg (1958) has described a form of extra-cellular cholesterinosis (Kerl-Urbach) which presents a picture resembling that of E.E.D.

4. The case briefly referred to above provides the proof that E.E.D. may develop with the histological picture of N.L. diabeticorum.

There are, therefore, four characteristic types which may be recognised and which share the histogenesis of this group of disorders. The histochemistry is still fragmentary. Should one from this argument conclude that N.L. is identical with a certain type of xanthomatosis ; or that E.E.D. is identical with N.L.?

We should further point out that from the point of view of pathogenesis the vascular lesions are sometimes not sufficient to justify an infective or dystrophic vascular origin of the necrobiotic foci.

Histology.

Our histochemical study is incomplete since the histochemistry of fatty substances is lacking. However, we have tackled the histochemical problem from a different aspect. The frozen sections were stained with Sudan III and we have also studied the staining reactions for mucin, PAS stains and examination by polarised light. These examinations were carried out with a view to confirming or otherwise the hypothesis of a disease in the strict sense of the term and of primary changes in the ground substance and with the object of deciding the importance of and the part played by infiltration of lipoid, glycogen and mucin. We were not able to decide upon any strict histological or histochemical criterion to enable us to differentiate N.L. from granuloma annulare and N.L. diabeticorum. Perhaps the term N.L. should therefore have a purely histological significance as indicating a primary lesion which is common to two or more dermatoses. The value of the histological picture is that it often serves to corroborate the clinical diagnosis. We will do no more than to emphasise the interest of a study of the histogenesis of this primary lesion. The cases we report do not allow us to draw any definite conclusions but bring out certain particular points.

We have investigated the molecular structure of the collagen with the aid of polarised light. Birefringence of the collagen bundles is one of their

fundamental properties and indicates the orientation and alignment of the long protein macro-molecules.

Inside early foci which are small but already well formed and sometimes considerably infiltrated with lipoid, birefringence of the collagen remains normal qualitatively and quantitatively. This birefringence disappears in the foci only gradually as they develop. It seems, therefore, that examination by polarised light more than histochemical methods allows us to conclude that collagen degeneration is a late phenomenon which occurs secondarily during the development of foci, whether these are of true N.L. or of granuloma annulare with secondary lipoid infiltration.

Finally there is the deposition of mucin, but this is found too inconstantly, in too small quantity and without sufficiently constant localisation for us to be able to consider that it is an essential part of the mechanism. In our view mucoid infiltration must be regarded as a secondary phenomenon, as indeed are the infiltrations with glycogen and lipoid.

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THE STRUCTURE OF COLLAGEN AND ELASTIC TISSUES IN UNPROCESSED SKIN.

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During the past few years biochemists have studied collagen by modern methods, and have come to regard this structure not as a mass of fibres embedded in ground substance, but as a mixture of polymers derived from a parent monomer. This monomer, or unpolymerized molecule, has been named tropocollagen by Schmitt and his co-workers (Schmitt *et al.*, 1955; Gross, 1957). The unit has a length of about 2000 Å, and is thought to contain only one, or a few, polypeptide chains, in cross-section. There is a strong tendency for end to end and lateral interaction of the particles which ultimately leads to the formation of fibres.

It is thought that this tropocollagen is laid down in the intercellular space of the dermis by fibroblasts, and fibres are then formed by a process of polymerization. The actual proportion of collagen existing in this dispersed or colloidal state is not known. Because of the ease with which polymerization takes place, fibres are rapidly formed by artificial means; even a weak solution of sodium chloride will cause the formation of fibrils from dermal extracts.

Histologists on the other hand have been convinced that collagen is entirely fibrous, the spaces seen between the bundles being filled with ground substance in the living skin.

In view of the modern biochemical findings it was thought possible that the mass of collagen bundles seen in routine histological sections might be artificially produced by the fixation and processing of tissue, and that these were not present as fibres in the living skin. This paper gives a preliminary account of work on the histological appearance of collagen in unprocessed skin, and of our attempts to orientate the collagen bundles before their formation by fixation.

Methods and Results.

The examination of unfixed skin is virtually impossible by routine procedures; we therefore developed a fluorochroming technique that could be applied to fresh skin. Biopsies were kept at 4° C until they were sectioned on a freezing microtome. The sections were fluorochromed with acridine orange (1 in 20,000) at 4° C in a specially constructed apparatus, mounted in distilled water and examined by fluorescence microscopy. Skin examined by this technique showed no evidence of the masses of collagen bundles seen in ordinary histological

sections. Fibres were present, but these were delicate green strands running through an apparently homogeneous blue collagen (Fig. 1). These fibres have been shown to be elastic tissue, as they are removed by elastase but not by collagenase.

For the purpose of studying elastic tissue as opposed to collagen it was found possible to use short alcohol fixation prior to freeze sectioning, for although this caused some flocculation of the collagen it did not interfere significantly with the histological appearance of the elastic tissue. When this homogeneous collagen was examined by polarized light it was strongly birefringent. This

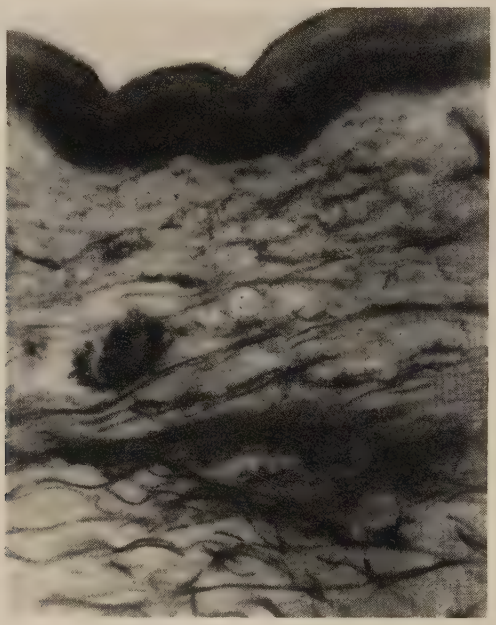


FIG. 1.—Fresh unfixed and unprocessed human skin of forearm. Numerous elastic fibres are clearly seen. (They are removed by elastase.) The collagen appears as a homogeneous background.

indicated that in the dermis there was a well orientated macromolecular system. It was thought possible that these orientated macromolecules were the precursors of collagen fibres.

It was soon realized that the site from which skin was taken, and the age of the patient, made a great deal of difference both in the amount of elastic tissue demonstrated and to its colour reaction. These differences may be even greater than those occurring in some pathological states of the dermis. Thus during the investigation of scleroderma, biopsies taken from the forearm showed a great increase in elastic tissue compared with control biopsies from the back. These fibres fluoresced red, and therefore differed from those of the control

biopsies ; nevertheless they were removed by elastase, and not by collagenase. When biopsies from the forearms of normal persons of the same age were examined, the same red elastic fibres were present. The chief difference was that in scleroderma there was more reduplication of the elastic fibres than in the controls. This difference due merely to the site of the biopsy is important when one remembers that our basic conception of the nature of elastic tissue is derived from the study of the ligamentum nuchae of the cow. These results show that there is very much more elastic tissue in scleroderma than was previously thought, and at least half of the apparently homogeneous collagen of this disorder is really elastic tissue.

A case of morphoea of the back was examined by these methods ; the elastic tissue fluoresced green as in normal skin from this region, but the fibres were thicker and more numerous.

A case of pseudoxanthoma elasticum showed gross changes in the elastic tissue which was not removed by collagenase, and only partly by elastase. The latter finding agrees with Findlay (1954) who reported that the elastic tissue in this disorder was more resistant to elastase than normal.

Orientation of the Collagen Bundles.

Assuming that the dermis in the living state is an orientated macromolecular gel, we should be able by physical methods to alter the orientation ; then on subsequent fixation and processing the fibres should have taken up the newly orientated arrangement.

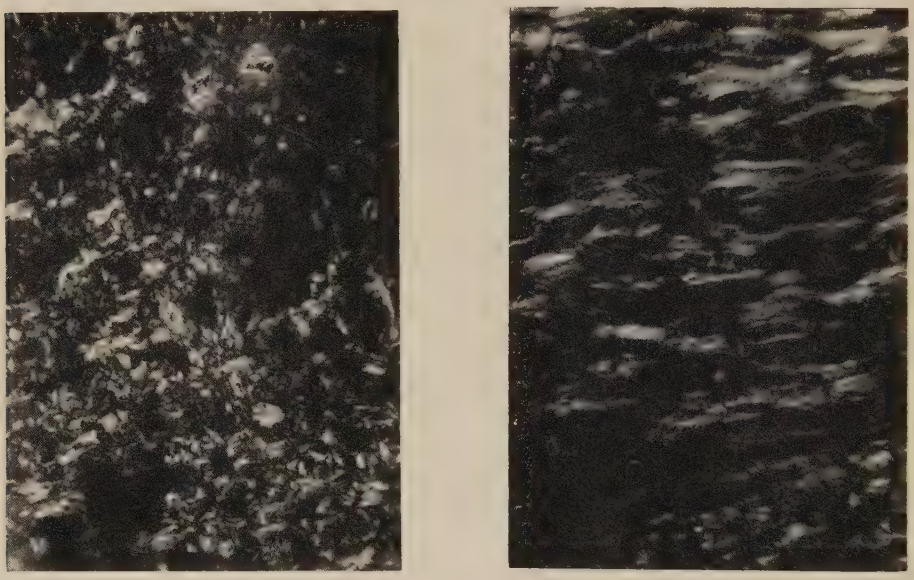
Attempts were made to change the orientation by passing an electric current through the dermis. On making and breaking the circuit, a lava-like flow of the dermis was observed under the microscope, but the prolonged passage of the current resulted in heating the tissue to levels which caused histological damage.

Further attempts were therefore made by first irradiating the skin with ultra-sonic waves before passing the current. Ultra-sonic irradiation was used in the hope of reducing the degree of polymerization already present in the collagen, and causing disorientation of the macromolecules, after which they could be realigned by the passage of a galvanic current in a predetermined direction. The frequency employed was 650 kilocycles per second, and the tissue was irradiated for about one hour ; an orientating current of 3 milliamps. was then passed for 10 to 15 minutes. The skin was then fixed, freeze-microtomed and examined by polarized light. Some reorientation of the collagen bundles was found to have resulted, and further work along these lines is being undertaken (Figs. 2*a* and *b*).

Conclusions.

It is thought therefore that the living dermis is probably a gel ; within this complex gel are orientated polypeptide macromolecules. These are the potential

collagen fibres, and are formed into fibres by the routine processing of skin for microscopy. The dermis is believed to be in a dynamic state, and capable of rapid adaptation to changing conditions. This view is supported by Jackson's work on the uptake of radioactive glycine into the dermis (Jackson, 1957). Elastic fibres run through the gel, but these are not necessarily elastic as a gel itself has elastic properties. It is thought more likely that they actually limit the extensibility of the dermal gel by acting as binding fibres. This concept is strengthened by the finding of dense elastic fibres in scleroderma.



(*a*) (*b*)

FIG. 2.—Normal dermis of guinea-pig. (*a*) Control : There is a random orientation of the collagen fibres. (*b*) Adjacent dermis after ultra-sonic irradiation and passage of a galvanic current. The collagen bundles have become orientated in the direction of the current. Polarized light.

The effects of fixatives, especially formalin, are of interest. Jackson believes that as polymerization of tropocollagen progresses there is an increase in the cross linkages between the fibrils, rendering them more stable and less soluble. Formalin is capable of developing cross linkages between adjacent amine and amide groupings. It reacts first with the amine group to form a condensation product which in turn links with the amide group with the elimination of water.

1. $R.NH_2 + HCHO \rightarrow R.NH.CH_2.OH.$
2. $R.NH.CH_2.OH + H_2N.CO.R' \rightarrow R.NH.CH_2.NH.CO.R' + H_2.O.$

It is therefore possible that formalin induces fibre formation from tropocollagen, and that fibres are thus formed during fixation that are not present

in the fresh dermis. Furthermore it has been shown that, during embedding, wax is forced between the bundles, and when the wax is dissolved in xylol, spaces appear. Thus both spaces and fibres seen in routine histological preparations are probably artefacts that do not exist in the dynamic colloidal state of the living skin.

I am most grateful to Dr. W. N. Goldsmith for his helpful advice. I also thank Mrs. Joan Hardy and R. I. Spearman, B.Sc. for their invaluable help with these investigations. Mr. A. Bligh kindly assisted in the production of the photomicrographs.

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INFLUENCE OF CERTAIN NEUROTROPIC DRUGS ON DINITROCHLORBENZENE ECZEMA IN THE GUINEA-PIG

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Paris.

The experiments here described were designed to investigate certain aspects of the role of the central nervous system in allergic dermatitis in the guinea-pig.

We accordingly established dinitrochlorbenzene eczema in the guinea-pig by epicutaneous applications and then studied the influence of neurotropic drugs on the course of the degree of sensitization as assessed by quantitative tests.

We will consider first some of the problems raised by these experiments.

Materials and Method.

One hundred and sixty-seven white guinea-pigs weighing between 400 and 700 gm. were studied in the present series. It was possible to follow the cutaneous reactivity for from four to eight months in 88 of them and only these have been included. The experimental animals were isolated in individual cages and fed at will, the room temperature ranging from 18 to 20° C. They were allowed several weeks to become accustomed to conditions in the animal house and to the person of the handler before being subjected to the experiments.

The allergen employed was 2-4 dinitrochlorbenzene (Prolabo) purified and dissolved in acetone. The solutions were renewed twice weekly and kept at 4° C. in the dark.

Sensitization of the animals was achieved by the daily application for from 12 to 18 consecutive days, of 0·05 c.cm. of 0·135 % solution of DNCB, applied with a pipette to the centre of a circular area of about 8 sq. cm. prepared on a flank with fine scissors and with no other epilating agents. The area of 8 sq. cm. is about the zone of spread of the quantity of solution employed and we were therefore able to know accurately the quantity of allergen applied per unit of surface.

When visible dermatitis had been obtained the guinea-pig was tested by the application of a similar quantity of the solution on an identical area on the opposite flank. The existence of sensitization was accepted when the first application to this flank provoked in 24 hours an erythematous reaction with or without crusting and oedema.

Once sensitization had been demonstrated we estimated its intensity by the

quantitative technique described by Frey (1951). For this purpose we used 6 to 8 areas of approximately 8 sq. cm., three or four on each flank, epilated with scissors. On the various areas are applied 0·05 cc.m. of solutions of 0·01, 0·03, 0·05, 0·1, 0·135, 0·150, 0·175 and 0·2% of DNCB. When a positive reaction is obtained on one of the surfaces we wait for its disappearance (2 to 7 days) before applying on another site the same quantity of the next lower concentration. The threshold of sensitivity corresponds to the lowest concentration capable of provoking a definite response in 24–48 hours.

Since the initial threshold does not necessarily prove to be stable the test must be continued for several weeks, usually from 4 to 6. We systematically checked the stability of the threshold over a period of four weeks and after this lapse of time were able to retain only 88 animals.

These animals were divided into three groups. The first served as the *control* and the spontaneous variations of the threshold were followed in each animal. The second group was subjected to the daily subcutaneous injection of 2·5 mgm. of *dexamphetamine* and of 5 mgm. of *caffeine*. The third group was subjected to the daily subcutaneous injection of 30 mgm. of *chloral hydrate*. In each of these groups the threshold was determined as described above.

Before presenting our results it will be useful to emphasize certain points in our technique. The quantity of allergen employed per unit of skin surface must be precisely known if one wishes subsequently to measure exactly the degree of sensitization of the animal. Although Rostenberg (1947), Rostenberg and Kanof (1941), Dunn *et al.* (1945), Nilzen (1952), Frey (1951), always recorded it carefully the majority of authors mention only the concentration, leaving in doubt either the quantity of solution employed or the area of skin to which it was applied. This lack of precision accounts for the divergences of opinion between authors concerning the maximum concentration which will not act as a primary irritant. Thus Frey (1951) with 0·2% claimed to obtain 100% of toxic dermatitis, Nilzen (1952) 17% and Baldridge and Kligman (1951) none at all. Under the conditions described we found that concentrations of up to 0·175% never provoke toxic dermatitis, whereas in a batch of 35 animals refractory to our technique of sensitization we six times obtained a primary reaction to a single application at 0·2%. Finally we noted that certain guinea-pigs which at the first or second application at 0·135% presented a slight erythematous reaction subsequently showed a higher threshold and failed to react at all even at 0·2%. This observation conflicts with the general view that the irritant concentration is constant and corroborates the observations of Chase (1941) and of de Weck and Brun (1956). It is evident however that above a certain concentration a toxic dermatitis results in nearly every case.

Study of the literature shows that with higher concentrations nearly 100% of animals could regularly be sensitized (Table I).

TABLE I.

Authors.	Concentration employed.	Test.	No. of guinea-pigs sensitized.
Nilzen (1952) . . .	30% Acetone .	0·1% Alcohol .	112/120
		0·1% Acetone .	100/120
Rostenberg (1947) . .	30% Acetone .	0·1% Acetone .	5/6
de Weck and Brun (1956)	1% Acetone (11 applic.) .	0·1% Acetone .	212/223
	1% Acetone (17 applic.) .	0·1% Acetone .	222/223
de Graciansky . .	1% Acetone .	0·135% Acetone .	15/15
	3% Acetone .	0·135% Acetone .	7/10

Our technique however reveals important individual differences in the rapidity, the duration and the degree of sensitization. The technique thus allows the application of experimental findings to man in whom one observes just such a wide range of response.

The test of sensitization which we have chosen is purely naked-eye. We considered this suitable because we have invariably worked with concentrations below irritant levels and because histological confirmation was obtained in four groups of animals which were excluded from our grand total because of the possible effects on the threshold of the biopsy and of the anaesthetic itself.

It is necessary however, if one wishes to use this test, to have several areas available so as to avoid the chronic infiltration which results from repeated applications. From this point of view the results obtained by Zeligman (1954) cannot be considered valid, nor those of Frey and Wenk (1955) who applied various concentrations simultaneously on different areas. It seems to us open to criticism to apply three different concentrations on the same day, for it is impossible to determine the interreaction between them ; such a technique may produce a summation of stimuli which would produce a misleading response.

The quantitative measurement of sensitivity described by Frey, which involves the successive application of different concentrations and known quantities, offers greater reliability than qualitative estimates of the intensity of the reactions obtained. The results obtained by Nilzen (1952), and by Frey (1948, 1951) and Frey and Wenk (1956) in animals, and by Ramos and Silva (1955) in man, support this view.

With this method we have observed that the threshold in each animal, once well established, is remarkably stable over a long period of observation or slowly rises. We have thus been able accurately to assess the effect of drugs.

RESULTS.

1. *Number of sensitizations obtained.*

Among 167 animals

42 (25%) could not be sensitized.

31 (19%) showed a continuously rising threshold and eventual loss of sensitivity.

94 (56%) became sensitized satisfactorily (six died during the course of the experiments).

2. *The course of sensitization.*

	25 Controls	37 Caffeine-Dexedrine	26 Chloral
Stable threshold	13 (52%)	9 (24%)	2 (7%)
Rising threshold	11 (44%)	2 (5%)	21 (82%)
Falling threshold	1 (4%)	26 (71%)	3 (11%)

Discussion and Interpretation of Results.

Allergic dermatitis in the guinea-pig is an individual phenomenon conditioned by the biological constitution of the animal. The technique of sensitization with low concentrations has enabled us and other authors to establish this fact (Table II).

Table II.

Authors.	Concentration employed.	No. of Applications.	Test.	No. of guinea-pigs sensitized.
Frey (1951)	0·1% Acetone	4–10	0·1—0·01% Acetone	54/56
Schepank (cited by de Weck and Brun)	,,	16–24	0·1 Acetone	0/26
de Weck and Brun (summer) (1956)	,,	11	,,	0/6
de Weck and Brun (winter)	,,	11	,,	7/9
de Graciansky	0·135% Acetone	12–18	0·135% Acetone	94/167

The Role of Neurotropic Drugs.

Various authors have studied the role of the nervous system in contact eczema in the guinea-pig (Charpy *et al.*, 1953; Miescher, 1941; Storck and Koella, 1952; Bohnstedt and Eichert, 1950; Ramos and Silva, 1955).

Guy (1952) in guinea-pigs previously sensitized, tried to increase emotional tension by depriving them of sleep for five days by repeated electric shocks associated with a loud noise. He thus obtained a considerably greater intensity of the reactions as compared with controls but the use of 1% DNCB in alcohol for the test makes the results difficult to interpret.

Polak (1957) investigated the role of inhibition and stimulation. Sleep, induced by Somnifaine for 21 to 28 hours, largely prevents the development of sensitization and also diminishes the intensity of the response to a test dose in animals which have been previously sensitized in the waking state. The stimulation experiments were carried out by sensitizing animals subjected either to permanent nonceptive stimulation (injection of turpentine into the

sole of the foot) or to repeated electric stimulation, or to Guy's technique of preventing sleep. He observed only differences which were minimal and of questionable significance in the period required for the development of sensitization. However, the author wonders, rightly in our opinion, whether sensitizing guinea-pigs with a strong concentration (5%) and the exclusive employment for the test of a concentration of 0·5%, might not fail to reveal slight modifications induced by changes in nervous function.

These results all point in the same direction as our own—heightening of sensitivity by stimulating drugs, lowering of sensitivity by sleep or sedatives—and show moreover that sedation impedes the development of sensitization.

At what Level did the Drugs Employed Act?

We chose these drugs for their action on the central nervous system, particularly at the cortical level, and for their lack of peripheral action. Caffeine is "a stimulant of cerebral function increasing the excitability of centres of perception and association and increasing the speed of conditioned reflexes." (Hazard). It is a peripheral vasodilator but exclusively of the coronary, cerebral, pulmonary and renal vessels. It has no cutaneous vasomotor action.

D-amphetamine acts through the reticular system of the brain-stem on the cerebral cortex at which level it provokes increased electrical activity. It has no peripheral sympathicomimetic action. (Hiebel *et al.*, 1954.)

Finally chloral, according to the dose employed, is a "simple hypnotic acting predominantly on the cortex or as a general anaesthetic." (Hazard.)

The effects observed by us on the threshold of sensitivity could certainly not be attributed to peripheral vascular changes—vasodilatation accounting for the increased intensity of the test and vasoconstriction for the reverse.

We are no doubt dealing with a modification of sensitivity by central nervous activity effects which could be predicted from clinical observations and the general laws of cortical function.

It is interesting to contrast these positive findings with the failure of attempts to modify sensitization tests to DNCB with antihistamine drugs given in almost toxic doses (Frey, 1948).

Conclusions.

The experiments here reported underline the *individual* character of the development of sensitization, its degree and its course in the laboratory animal. This feature brings the conditions of experiment very close to those of contact eczema observed in man.

Further, the influence of centrally acting drugs on the development of the allergic state shows that the central nervous system modifies the response to the allergen and that it represents an important component of what it is customary to call the soil.

These conclusions are valid no matter what may be the mechanism determining the eczema, and whether or not one accepts it as an antigen-antibody reaction.

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ANGIOKERATOMA CORPORIS DIFFUSUM.

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This paper is an account of three members of a family with angiokeratoma corporis diffusum, comprising two males and one female. In the last the diagnosis was made post mortem.

Case Reports.

Case 1.—A man aged 39.

History.—This patient was first seen in September 1956. He had had a dull occipital headache for the preceding three weeks, worse during the early hours of

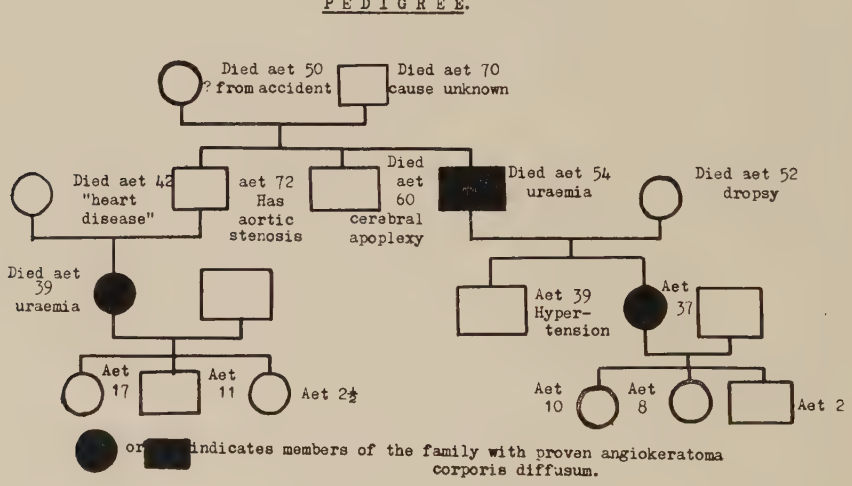

Fig. 1.

the morning and easing during the afternoon. There was a history of migrainous headaches occurring at about two-monthly intervals for the past year, each attack lasting about a quarter of an hour and accompanied by transient aphasia and some nausea. Since childhood he had noticed a symptomless rash, particularly on the elbows and thighs. His ankles had swollen only during the summer for some years, but this swelling had persisted throughout the previous winter. He had also become progressively more thirsty for the past two or three years, with nocturnal frequency for the last three months. There was no discomfort or paraesthesia in the legs and he felt well in himself.

Examination.—Fit-looking, well-built man with typical angiokeratoma corporis diffusum. Small lesions on the lips, backs of elbows and fronts of knees; larger lesions on penis, scrotum and medial aspect of thighs. Tongue and buccal mucosa normal. Lichenified dermatitis on left calf and splinter telangiectases in nails.

In addition he had slightly sallow skin with brown eyes and black hair. Slight pitting ankle oedema, right more than left. All pulses palpable ; B.P. 210/120. Hypertensive retinopathy with diffuse flat wedge-shaped corneal opacities. No other physical abnormality.

Investigations.—Urine : Specific gravity constant at 1008. Albumin + +. No other abnormal constituents. Urine chromatography : Small quantity of normal amino-acids only. Blood urea : 45 mgm.% (mean of 4 estimations).

Water deprivation, creatinine, pitressin tannate concentration tests all indicated impaired tubular function.

Plasma proteins and electrolytes, serum calcium and cholesterol were normal. The electrophoretic pattern of the plasma proteins was normal but lipoprotein electrophoresis showed an increase in beta-lipoprotein.

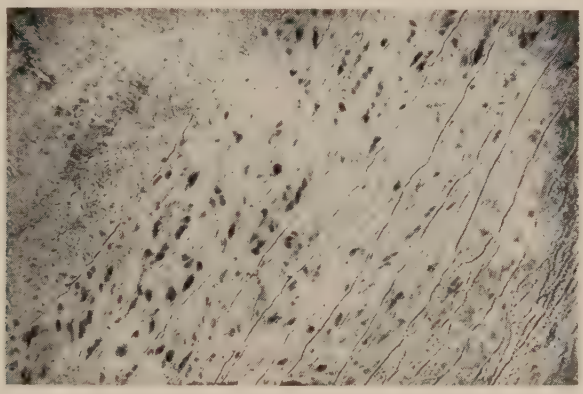

Fig. 2.—Section of artery from Case 1 showing phospholipid in medial muscle fibres. Sudan Black B.

Sweat gland investigation (both by heating the legs and with intradermal carbachol) showed many fewer active sweat glands than normal.

Complete blood count and skiagrams of chest and skeleton were normal.

Electrocardiograph showed left ventricular hypertrophy.

His general condition deteriorated rapidly and he died in uraemia in January 1958. A complete post mortem examination was carried out and the findings will be reported more fully by Shorter (1958).

Macroscopically there was evidence of acute bronchitis, bilateral pulmonary oedema and pleural effusion. The heart showed gross hypertrophy of the myocardium of the left ventricle, but no other abnormalities. In the intima of all the major arteries with the exception of the aorta, small yellow streaks were observed, differing slightly in colour from atheroma. No abnormalities were detected in any of the major veins. Both kidneys showed granularity of the cortex with indistinct cortico-medullary junctions. The capsules stripped with difficulty. In the sub-cortical tissue of the left frontal lobe of the brain and in the basal ganglia were many small areas of cystic softening, with no evidence of recent or old haemorrhages. Superficial dystrophic corneal changes were also observed.

The tissues obtained at necropsy were fixed in 10% neutral formalin. Paraffin-blocked material was sectioned and stained with haematoxylin and eosin. To demonstrate the presence of phospholipid, tissues were stained with Sudan Black B (Pittelkow *et al.*, 1957). Unstained sections of selected tissues were examined polarisopically to study the vacuolation in the smooth muscle of vessels and frozen sections of all the material were stained for neutral fat with technical Fettrot (Ciba).

Six major arteries were examined and in all the medial muscle fibres showed vacuolation with nuclei varying in size and shape, some being very large. The presence of lipoid in these vacuoles was confirmed by examination under polarized light and with Sudan Black B (Fig. 2). In addition, there was patchy atheroma. Similar vacuolation was found in smaller vessels in many other parts of the body, but no evidence of any lipoid in the walls of the veins. This may, however, have been caused by a failure to add 1% calcium chloride to the formalin fixative and the resultant loss of lipoid during the process of fixation. In addition, the arterioles throughout the body showed fibrinoid degeneration indistinguishable from that seen in patients with malignant hypertension. The myocardium of the left ventricle showed similar vacuolation and phospholipid to that observed in the medial musculation of arteries.

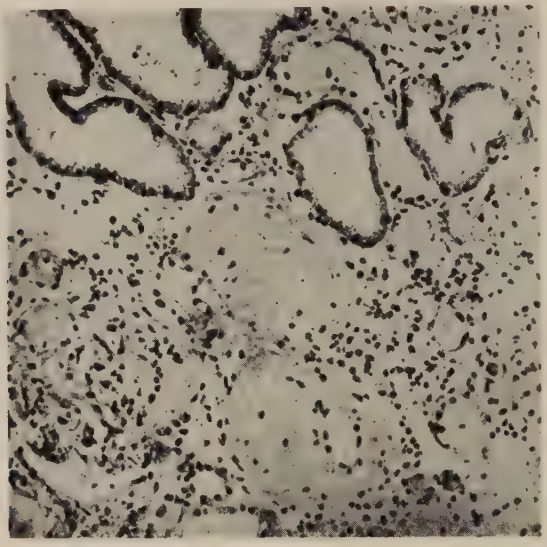

FIG. 3.—Glomeruli replaced by structureless collagenous masses. H. & E.

The kidneys showed fibrosis and non-specific chronic inflammatory-cell infiltration with marked reduction in the number of glomeruli, most of them being represented by structureless collagenous masses (Fig. 3). In the surviving glomeruli were varying degrees of ischaemic change with occasional areas of fibrinoid necrosis. Vacuolation identifiable as phospholipid with Sudan Black was demonstrated in the glomerular tufts and tubules (Figs. 4 and 5). "Fibrinoid" necrosis of small arterioles and intimal hyperplasia due to malignant hypertension were also prominent. As in other parts of the body, phospholipid was present in all these vessels.

The skin lesions showed hyperkeratosis with dilated blood-containing spaces in the upper corium with intact endothelial linings showing no evidence of vacuolation (Fig. 6). The sweat glands were normal in number and appearance. No cutaneous aneurysms were found, although vacuolation and phospholipid was present in the deeper arterioles. The basal ganglia showed phospholipid in the walls of the small vessels but there was no conclusive evidence of similar accumulations in nerve cells in any part of the nervous system. The appearances of the areas of cerebral softening were those of ischaemic degeneration.

Sections of the eye showed marked thickening of the corneal epithelium due to hyperplasia of the epithelial cells, particularly centrally. At scattered points

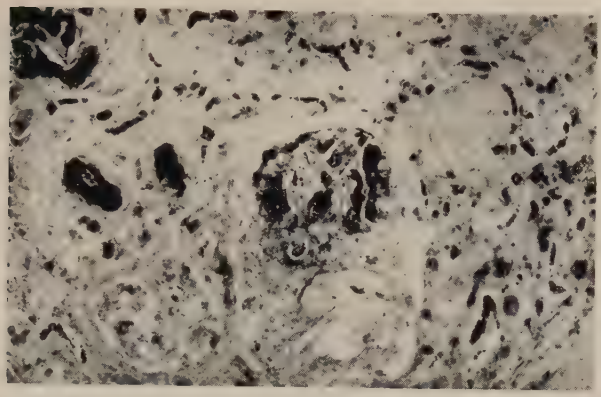

FIG. 4.—Phospholipid in a surviving glomerulus. Sudan Black B.

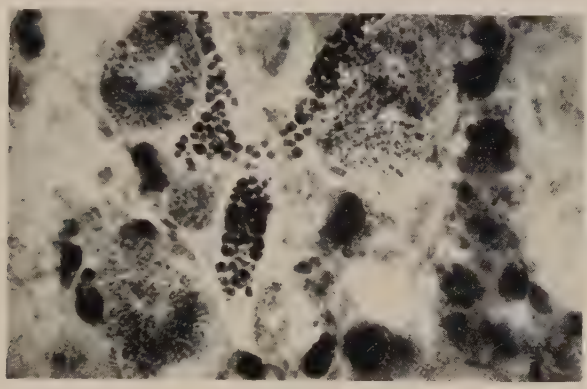

FIG. 5.—Phospholipid in renal tubules. Erythrocytes contained in vessels show clearly. Sudan Black B.

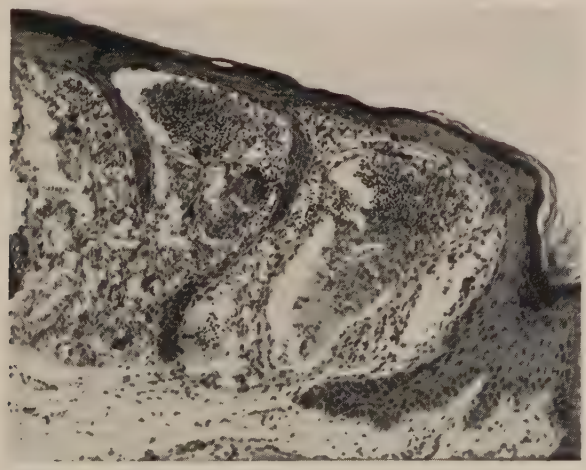

FIG. 6.

throughout the epithelium there were well-demarcated islands of swollen oedematous cells and it is presumed that these were responsible for the corneal opacities seen in life. The underlying Bowman's membrane and substantia propria were normal but there was an unusual degree of cystic degeneration in the retinal periphery.

No evidence of vacuolation or abnormal phospholipid deposit was found in any other part of the body.

Case 2.—A man aged 35.

History.—This man, a first cousin of Case 1, was seen in November 1956. He gave a history of symptomless pinhead spots on buttocks, scrotum and elbows since childhood, varying in colour from purple to almost black. He said that he had never sweated and had become more thirsty during the past six months. An ulcer had been present on the left ankle for the past twenty years following a kick, and on the right ankle for the past six years. This more recent ulcer had apparently occurred spontaneously. These ulcers had been grafted about two years previously but the grafts had rapidly broken down. He had not noticed any ankle oedema before the onset of the ulceration. He gave no other relevant past history.

Examination.—Ill-looking man with angiokeratoma corporis diffusum on buttocks, hips, scrotum and penis, with a few slightly smaller lesions on the arms, backs of elbows and hands. No lesions on lips, buccal mucosa or under the nails, but originally a mild telangiectasia of face and ears. Sallow skin, brown eyes and brown hair. The hands somewhat flattened and spade-shaped. Short stubby toes, the clinical appearances suggestive of chronic lymphatic oedema. Bilateral pes cavus, worse on the right than the left. Bilateral firm painless enlargement of superficial and deep inguinal glands. A deep ulcer about 10 cm × 3 cm. was present on the medial aspect of the right leg. All pulses present and equal. B.P. 125/70. Retinal arteries tortuous, especially the smaller branches, with marked beading of retinal veins. Superficial dystrophic corneal changes of unusual morphology. No other physical abnormality found.

Investigations.—Urine : Specific gravity constant at 1008. Albumin +. No other abnormal constituents. Blood urea : 28 mgm.% (mean of 4 estimations).

Water deprivation, creatinine, pitressin tannate concentration tests all indicated a moderate impairment of tubular function.

Plasma proteins and electrolytes, serum calcium and cholesterol were normal. The electrophoretic pattern of the plasma proteins showed low gamma-globulin and a prominent extra band between beta and gamma portions, a double beta-globulin band, the slower component being strikingly dense. Lipoprotein electrophoresis showed a normal pattern ; the beta-lipoprotein travelled with the faster of the two beta-globulin bands.

Sweat gland investigation (both by heating the legs and with intradermal carbachol) showed many fewer active sweat glands than normal.

Blood count : November 1956—normal. April 1958—Hb 68%. P.C.V. 32%. M.C.H.C. 31%. Reticulocytes : less than 1%. W.B.C. 7300/cu. mm. (Neutros. 60%, lymphos. 36%, eos. 4%). Film : No R.B.C. abnormalities detected. E.S.R. 86 mm. in 1 hr.

Skiagrams of chest and skeleton—normal.

Electrocardiogram—normal.

Skin biopsy—The changes did not differ materially from those in Case 1.

Renal biopsy—The glomeruli showed uniform doubly refractile vacuolation of the epithelial cells (Fig. 7). Occasional cells of Bowman's capsule and many in the ascending loops of Henle and distal tubules showed a similar change. The proximal tubules by contrast showed no significant abnormality. A piece of interlobular artery included in the section showed marked intimal thickening with oedema and degeneration of the medial muscular coat.

Case 3.—The mother of Case 2 and the aunt of Case 1. She died in the Neurosurgical Unit of St. George's Hospital, London, on 12 : viii : 49, having been admitted the previous day with a history that she had been in coma for the past few days. No definite cause for the coma was found before death and her blood urea just before death was 80 mgm.%. At the post-mortem examination, gross enlargement and tortuosity of the basilar artery was observed. Professor Crawford has also kindly made available sections of the kidney. These show changes comparable with those of her son with, in addition, a wedge-shaped area of cortical fibrosis with glomerular fibrosis, chronic inflammatory-cell infiltration and marked narrowing of interlobular arteries as seen in chronic pyelonephritis. There is no record of any rash, and her daughter, who is well acquainted with her brother's rash, is sure that her mother's skin was clear.

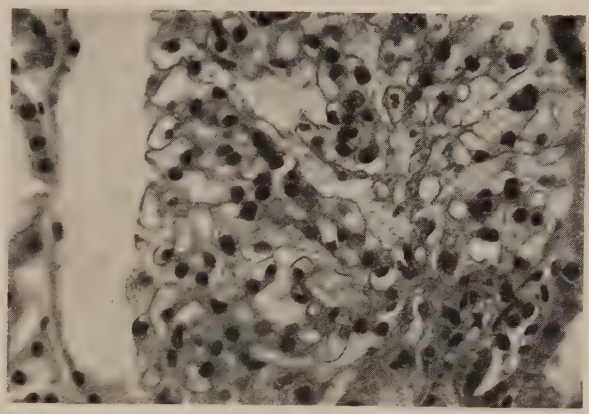

Fig. 7.—Uniform vacuolation of the epithelial cells of the glomeruli. H. & E.

Angiokeratoma corporis diffusum appears to be quite distinct from other forms of angiokeratoma, although the scrotal lesions in this disorder may be clinically indistinguishable from the comparatively common angiokeratoma scroti. Without thorough examination it is easily possible to overlook the more widespread but often inconspicuous lesions of angiokeratoma corporis diffusum. I have been unable to discover whether angiokeratoma scroti has been fully studied, although there is little doubt that it is much commoner and quite distinct from angiokeratoma corporis diffusum.

The literature on this disorder, which appears essentially to be a lipoid storage abnormality, has been well reviewed by Fessas, Wintrobe and Cartwright (1955) and particularly by Ruiter (1954, 1957) who has done much excellent work on the disease since it was first described by Fabry in 1898.

Investigation of the family now reported has not shed any light on the nature of the disorder. There are, however, two matters which are perhaps of interest. The first is what appears to be the early change in the kidney as shown by the renal biopsy of Case 2, namely, the distension and vacuolation of the glomerular tufts and distal tubules, the proximal tubules apparently being spared until the later stages of the disorder. Very occasionally a similar change is seen

in the glomeruli of patients suffering with a severe nephrotic syndrome (Allen, 1951), but it is usually limited to a few isolated cells. Involvement of glomerular cells in lipoid storage diseases is also observed occasionally in Nieman-Pick's disease and in certain types of xanthomatosis. Extensive vacuolation of the glomerular cells combined with a similar change in the cells of the distal tubules, however, does not seem to have been described in any other condition than angiokeratoma corporis diffusum.

Second, this appears to be the first recorded case of this disorder in a female, and who is said to have had no skin lesions. Since the renal changes are often non-specific with the exception of the vacuolation which is easily overlooked at a routine examination, it is possible that angiokeratoma corporis diffusum may be more common in women than has hitherto been suspected, particularly if, as appears probable, the disorder may exist in the female without skin changes.

It has not proved possible to investigate further the nature of the hypertension in the sister of Case 2, or of the aortic stenosis in the mother of Case 1.

No histological or physiological cause could be found for the malfunction of the sweat glands, which appeared to be normal in appearance and number.

No definite evidence of the mechanism of formation of the angiokeratoma was found, although as Ruiter suggests, the lesions appear to be essentially telangiectases rather than a new growth of blood vessels.

The exact nature of the lipoid is still uncertain. In a patient described by Scriba (1951) there was said to have been ten times the normal content of diamino-phosphatides in the cardiac muscle and according to Kuhnau these differed only in solubility from sphingomyelin. Silicic acid chromatography of an extract of the liver from Case 1 showed no evidence of increased sphingomyelin.

I wish to thank Dr. M. S. R. Hutt for his help with the histology, Dr. A. Herxheimer for investigation of the sweat glands, and Dr. J. A. Lovern for his help with silicic acid chromatography.

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BENIGN MUCOSAL PEMPHIGOID

DERMATITE BULLEUSE MUCO-SYNÉCHANTE ET ATROPHIANTE

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At the meeting on 9 February 1956 I proposed to the French Society of Dermatology that the name *Dermatite bulleuse muco-synéchante et atrophiante* be substituted for that of " ocular pemphigus ". This term seemed to me preferable as it separates the disease as a clinical entity and, in the absence of specific histological, biological or bacteriological criteria, it defines thé essential clinical features. The re-naming of a disease long familiar demands an explanation. This I now propose to give.

Ocular pemphigus has in recent years been excluded from the true pemphigus group and grouped with dermatitis herpetiformis, especially since Civatte's work has allowed histological differentiation between pemphigus and dermatitis herpetiformis. Histological studies undertaken on these patients reveal a complete absence of acantholysis and show sub-epidermal bullae with all the features of dermatitis herpetiformis.

However, I can produce several arguments which seem to refute this classification. The clinical features and the course of this disease are such that it is no longer possible to identify it either with pemphigus vulgaris or with dermatitis herpetiformis. This concept has already been supported by Lever (1953), Church and Sneddon (1953), Cordero and Cerboni (1949) and many others.

The clinical features of benign mucosal pemphigoid are, in fact, quite distinct :

It is an eruption with but few cutaneous bullae, affecting chiefly the mucous membranes and usually, but not invariably, the conjunctiva. On the skin it sometimes leaves scars and on the mucosae leaves either adhesions or sclerosis and atrophy. The course is benign and the prognosis is therefore determined by the extent to which function is impaired.

Although Lever separates ocular pemphigus from the other bullous eruptions and accords it the status of a disease entity, he does not mention all the major clinical characteristics in his publications. To identify his " benign mucous membrane pemphigoid " Lever retains only three criteria : The benign course ; the predilection for mucous membranes ; and the tendency to produce scarring.

These, however, are not all the essential criteria. It seems to me, in fact, that other more pathognomonic clinical features deserve to be included—in particular : The progressively cicatrising course and the clinical appearance of the bullous eruption on the skin and mucous membranes.

These features, which have been enlarged on by Hardy (1956) in his thesis, serve to strengthen the position of the " autonomist " school.

Clinical Description.

Ocular lesions.—I will not dwell upon the ocular lesions. They are the best known and have been most studied, especially by ophthalmologists. The signs of ocular involvement are easily recognised ; they lead in most cases by stages to eventual blindness from symblepharon and corneal opacities.

This ocular involvement determines the functional outcome because as a rule both eyes are involved, simultaneously or consecutively. The first sign is a rather non-specific conjunctivitis which is sometimes accompanied by a viscid, yellowish secretion. On close examination at this stage bullae can be detected on the bulbar conjunctiva. The bullae are often overlooked even when they are present because of poor or inadequate observation. They occur on the lower third of the bulbar conjunctiva or less commonly on the tarsal conjunctiva, as translucent, rounded elevations. Each is surrounded by a very vascular, slightly oedematous halo.

More often the lesions found at the first examination are already cicatricial. The conjunctival sac is then shallow and synechiae stretch between the bulbar and tarsal conjunctivae. Traction on the lid reveals a vertical or oblique adhesion which is fixed to the bulbar conjunctiva and forms a partial symblepharon of the lateral angle of the lower part of the conjunctival sac. As the bullae recur in the same site the adhesion extends to form a fold of conjunctiva which moves with the eye. This fold forms a vertical membrane which as the eye moves covers and uncovers part of the conjunctiva like a transverse lid, reminiscent of the nictitating membrane of certain animals.

At the same time the surface of the cornea becomes epithelialised, dry and opaque and corneal microscopy shows interstitial vascularisation of its deeper parts.

The synechiae progress and lead to complete fusion of the eyeball to the lids. After several years symblepharon produces complete blindness, as both eyes are usually involved. In the final stages the eye shows the classical picture which has been called " the statue eye ", often complicated by xerosis and painful trichiasis.

Already, therefore, the two aspects of the disease, sclero-atrophy and synechiae are apparent. Sclero-atrophy occurs when there is no contact of the two mucosal surfaces, whereas if they are in contact fusion occurs, i.e. synechiae, and it is on this that the entire course of the disorder depends.

Mucosal lesions.—Many authors have noted the association of ocular lesions with involvement of other mucosae. This association is so common that one wonders if thorough examinations have been carried out by those ophthal-

mologists in whose reports it is not mentioned. All the mucous membranes may be involved, singly or simultaneously.

The *buccal mucosa* is the most frequently affected. The bullous lesions present no characteristic features. They are transient bullae which go on to form relatively painless erosions (perhaps differing, in this respect, from those of pemphigus). These are often chronic and *fixed*, may produce scarring, and disappear, only to recur at variable intervals, nearly always in the same site.

This constancy of site, because of either slow healing or recurrence, is a distinctive feature of this bullous eruption. The recurrence of the bullae *in situ* results, as in the conjunctiva, either in synechiae if there is contact of the two mucosal surfaces, or in atrophic scarring if there is not.

The *nasal mucosa* is nearly always involved at the same time. Routine examinations should be carried out to detect an atrophic rhinitis with crusted erosions and synechiae.

The *mucosae of pharynx and larynx* are also involved with consequent atresia, either by sclero-atrophy or by synechiae ; the soft palate or the posterior pillars may become fused to the pharyngeal wall or scar tissue may destroy the soft palate or uvula.

Many of these patients complain of dysphagia. This may be due to active lesions or scarring of the pharynx but also to *oesophageal lesions* which may necessitate gastrostomy. Routine studies of the oesophagus in these patients are thus necessary.

The *genital mucosae* are electively involved, and recurrent bullae result in synechiae or sclero-atrophic scars, which produce balanopreputial adhesions, adhesions of the labia minora to the labia majora, and atresia of the vagina or of the urethral orifice leading to difficulty in micturition and necessitating dilation.

Finally, the *anal mucosa* can also be involved.

This characteristic tendency to form synechiae must be emphasised because the bullous and scarring process can affect the mucous membranes and yet spare the eye for many years ; it may never lead to conjunctival involvement, as in a case reported by Gaté (1936). Hence the importance of recognising those cases without ocular involvement in order that treatment may be instituted with the object of preserving the eye.

Cutaneous lesions.—The clinical study of the cutaneous manifestations is particularly instructive because the evolution is more easily followed. Certain constant characteristics of the cutaneous bullae illustrate the distinctive and specific tendency to form scars in the same fashion that the mucosal lesions form synechiae.

Although Lever was one of the first to give an authoritative description of ocular pemphigus as a disease in its own right by insisting on the tendency of the lesions to produce scars (which others before him had suggested), it appears

that first Steiner (1869), and later Adler (1876), Matschke (1890) and Ramel (1924), have the priority in the description of pemphigus with scarring. Not all the cutaneous bullae inevitably go on to scarring—indeed, only the chronic fixed bullae which form crusted, ulcerated lesions ultimately result in this. Some skin bullae " lead to necrosis involving the whole thickness of the corium and leave scars behind them " (Matschke, 1890).

The fundamental characters of the cutaneous eruption are : The recurrence of the bullae in the same sites ; the chronicity of some of the bullae, which form crusted ulcers and leave scars ; and the rarity of cutaneous bullae.

The fixity of the bullae is quite remarkable and is easily observed on the skin. They often remain crusted for months or even years, showing no tendency to epithelialisation. One of our patients presented a fixed crusted ulcer overlying the patella for two years before the first signs of ocular involvement appeared.

Sometimes the erosions which follow the bullae heal, only to recur repeatedly in the same place. It is understandable that such lesions should in the long run leave sclero-atrophic scars. Cutaneous adhesions have never been reported, but the distribution of the bullae does not lend itself to this. However, it is not impossible to imagine that they might occur when bullae arise in skin folds, e.g. inguinal, submammary or interdigital.

The *distribution* of the bullae is characteristic. Especially involved are the centre of face and sides of the nose, the periorbital regions, the periumbilical and supra-pubic regions, and the shaft of the penis.

They present in these regions either as crusts following bullae or as crusted ulcers. Beneath the crust is either an erosion or a rounded haemorrhagic ulcer. Admittedly the bullous eruption can occur elsewhere, on the limbs, the thorax or the scalp, but in general it is localized and *circumscribed.*

The rarity of cutaneous bullae gives this eruption a distinctive character. Although several reports mention a profuse eruption resembling dermatitis herpetiformis, in most cases the bullae are few in number (two to five) and often there is but one fixed lesion. It is then that the correct interpretation of the significance of this bulla becomes important.

The scarcity of bullae in benign mucosal pemphigoid is such that 70% of patients never present any skin lesions. Nikolsky's sign is inconstant but has been reported in several cases. When present, it is found especially at the edge of the areas where the bullae occur.

General Signs.

The general condition of these patients remains consistently good. A most characteristic feature of the disorder is that, although it may last for many years, it does not affect the general health until adhesions in the viscera produce severe functional disturbances—strictures of the oesophagus, pharynx, meatus,

etc. These complications, with attendant malnutrition and cachexia, determine the prognosis for life, but they are essentially only mechanical. However, certain reports mention impairment of the general health, which we have not ourselves observed.

No biological tests provide any useful support to the hypothesis of an autonomous disease. Blood eosinophilia and the test for sensitivity to iodides, which was carried out by Church and Sneddon, have not given any conclusive results.

Histology.

Histological studies of the bullae should be viewed in the light of Civatte's work on the general diagnostic criteria of bullous eruptions.

However, this work has contributed towards the false integration of benign mucosal pemphigoid with dermatitis herpetiformis on the basis of the single fact that the bullae are *subepidermal*, situated beneath an epidermis which is raised up entire and unaltered. There is *no acantholysis*. All these are the histological features of dermatitis herpetiformis. However, there is a polymorphic infiltrate in the underlying dermis which is denser than that usually seen in dermatitis herpetiformis and in which plasma cells often predominate.

If the biopsy is taken from a long-standing crusted ulcer the histological picture has special features : The epidermis is hyperplastic with a tendency to vegetation, with formation of horny cell nests and with a few cells showing individual keratinization (a pseudoepitheliomatous picture). This histological appearance once misled us into using radiotherapy.

The Tzanck test never shows the large deformed malpighian cells of pemphigus but only normal blood cells and eosinophils.

This study has allowed ocular pemphigus to be separated categorically from the large group of pemphigus. No proven case has shown an intraepidermal bulla with acantholysis. This was the first point to be established. Second, the fact that the bulla has the histological features of dermatitis herpetiformis does not imply absolutely that ocular pemphigus is a dermatitis herpetiformis localized to the eye, as some authors have claimed. Although both have a subepidermal bulla without acantholysis one cannot base a logical, firm and reliable deduction on this single fact. There are limits to the value of histology.

I will not dwell further on the nosological position of benign mucosal pemphigoid which we have discussed elsewhere (Degos, Lortat-Jacob and Hardy, 1957).

Bacteriological and virological investigations have all been negative. We have recently undertaken cultures in hens' eggs of fluid from the bullae and of blood from three of our patients. They were all negative.

It seems to me, therefore, in complete agreement with Lever, Church and Sneddon and others that on clinical grounds alone benign mucosal pemphigoid should be considered an autonomous clinical entity on the basis of the character

of the eruption and its distinctive course. The clinical picture, as I have described it, is sufficient in my opinion to individualize the disease on purely clinical grounds, since no biological, bacteriological or histological criteria are available.

The clinical picture is made up by the association of :

(i) *Ocular lesions*—known to all under the name " Ocular pemphigus ".

(ii) *Mucosal lesions* in the form of recurrent bullae progressing to produce atrophic scarring and giving rise to cicatricial adhesions, synechiae and stenosis.

(iii) *Skin lesions*, recurrent bullae, which are distinguished from other bullous eruptions by their long duration in the form of chronic crusted ulcers, by their tendency towards scarring, by their fixity and by their rarity.

(iv) *Good general condition* and good prognosis for life until the appearance, always possible, of pharyngeal or oesophageal stenosis.

Treatment.

The successive treatments tried in this disorder are in general ineffective. Aureomycin seems not to have any favourable effect, and sulphapyridine rarely leads to any notable improvement ; sulphones do not seem to have been tried.

Systemic steroid therapy should be given a trial. The mere fact of its good effect in other generalized bullous eruptions should lead one to try it. Under its influence cutaneous bullae often disappear, although the effect on the mucosal lesions is less evident. It does not check the progress of the ocular lesions. On the other hand subconjunctival injections of cortisone are rapidly effective. The conjunctivitis clears up and bulla formation ceases. The effect does not seem to be lasting and relapses usually occur on stopping the injections. Hydrocortisone eye drops, although effective, are much less so.

Bolgert *et al.* (1954) have advised intravenous injections of copper. This treatment can be a useful adjuvant.

In the absence of all treatment the progress of the disease may be arrested spontaneously. It is in these cases that corneal grafting can be tried. (Degos *et al.*, 1957).

In the light of these arguments it seems difficult to justify the name " ocular pemphigus ", when ocular lesions are only one clinical manifestation of a widespread disease which can no longer be included in the pemphigus group.

Furthermore, Lever's term " benign mucous membrane pemphigoid " is unsatisfactory. Although this disease chiefly involves the mucous membranes, the restricted meaning of this designation fails to draw attention to the possible characteristic skin involvement which over a period of years may be the sole manifestation.

These are the clinical reasons which have led me to name this disease *dermatite bulleuse muco-synéchante et atrophiante*. It has the advantage of stressing the simultaneous involvement of the skin and mucous membranes, and more especially of emphasizing the characteristic course of this disease.

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URTICARIA PAPULOSA.

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Papular urticaria is well known to all of us as a definite clinical entity affecting young children in particular. We may differ in the name, but for the purpose of this short paper I regard the terms strophulus, prurigo-strophulus, prurigo simplex *aigu de Brocq*, lichen urticatus and papular urticaria as synonymous.

You will all agree with the classical clinical description in text-books of various authors—an urticarial flare, resembling that seen after injection of a minute drop of histamine into the skin, lasting for a few hours and then followed by a small papule which is surmounted by a vesicle. These small elements may persist in an active and irritable state for about three days and finally subside leaving a small pigmented spot. They may become crusted, haemorrhagic or infected after scratching by the patient. An occasional larger blister may be seen. The site of the eruption on legs, thighs, body and arms is quite typical and the recurrent nature of the disease is characteristic. It may last for several years. The number of individual spots is variable and all the different types may be present at one time. Irritation is a prominent feature and results in many sleepless nights.

The children who have urticaria papulosa are almost without exception, as Darier (1928) has written in his book, healthy in every way and do not suffer from symptoms of alimentary disturbance. This idea that the disease is due to disorders of digestion or follows the eating of certain articles of food is often suggested by the parents or even by the doctor. This could not be proved in a controlled scientific study.

In Great Britain and the United States of America work has been done over the years which indicates that it is due to parasitic infestation rather than allergies or other factors. First Hallam (1927, 1932), then Tate (1935), and more recently Rook and Frain-Bell (1953) have observed that children taken into hospital become free from their spots very quickly without treatment and do not develop any new ones as long as they remain in hospital. This suggests quite clearly that the eruption is due to something in their home environment. Then there is the work of Dietrich and Hamburger (1937) who found that fifty children with urticaria papulosa were sensitive to either bed-bug bites or flea bites. Later Blank, Shaffer, Spencer and Marsh (1950) tested thirty children who had urticaria papulosa with flea antigen and bed-bug antigen ;

77% were sensitive to one or both of these antigens, but only two out of 124 control subjects were sensitive.

Rook and Frain-Bell (1953) give a most complete account of the literature and much evidence which leads them to the conclusion that most cases of urticaria papulosa are the result of an acquired sensitivity to the bites of certain insects, particularly fleas and bed bugs.

My own interest in this subject began independently some time before this and consisted first of all in taking scrapings from papules and vesicles of papular urticaria. Many hours were spent searching for some possible cause of parasitic origin in the skin itself but this was in vain. Still convinced that the disease was unlike true urticaria but resembled scabies in other respects I called on a colleague from the Department of Zoology at Durham University, Dr. Burtt, an entomologist, and we planned visits to the homes of the children suffering from urticaria papulosa.

The scattered nature of the eruption in our patients and the presence of a central punctum in many of the urticarial lesions pointed to the possibility of bites from fleas or bed bugs. Many visits to homes followed and these were never without interest to both of us. Most of the sufferers came from poor houses in the oldest parts of the city of Newcastle upon Tyne, but we found that the disease may also affect people living in the best possible conditions, sometimes in new houses. We soon learnt that it is necessary to take a most careful history, to be most persistent in our enquiries and never to be put off by the fact that there are no animals in the home.

We encountered much scepticism from parents and from some doctors. We were frustrated on more than one occasion in our search when we found that if we proceeded relations in the family life would become strained or there was a possibility that the landlord might ask the family to move house if questions were asked about his pet animals. This accounted for several inconclusive results of treatment.

Amusement was not lacking, as in these three cases :

A boy aged seven had suffered repeated attacks of urticaria papulosa for six years. The family lived in the kitchen of an old, cold house because this was the warmest room. The grandmother sat on a rocking chair most of the day as she was feeble and suffered from rheumatism ; when she went to bed, the cat occupied the chair. Dust samples were taken from the cushion on the chair and were found to contain living larvae and eggs of the cat flea which were incubated and later identified. The grandmother had, in fact, acted as an excellent incubator by sitting constantly on the chair.

The cat was not permitted to sleep in the kitchen at night or to rest on any chairs. A box was arranged in the scullery and this and the cat were dusted regularly with pyrethrum powder. The child obtained relief for the first time in six years.

A second case is of a baby in an upstairs apartment who occupied the perambulator during the day but two cats belonging to the landlady slept in it at night because

it stood in the passage downstairs. The cats could not be treated as the mother of the baby thought she would lose her home if she mentioned it.

On a third occasion Dr. Burtt had to climb through a trap-door situated right above the platform in a meeting hall to investigate a pigeon loft. When he lifted the wooden door showers of bird lime descended on us both and scattered all over the platform and from this we collected material containing the pigeon flea.

The methods used in the collection of dust samples and subsequent incubation of these at the correct temperature and humidity have already been described (Bolam and Burtt, 1956). Attention is directed to chairs, sofas, rugs, beds and the fireside apart from the obvious place where the animals sleep. Examination of the actual animals in and around the home does not prove very helpful, but in this connection a further case history is of interest.

A girl aged three years had attacks of urticaria papulosa for two years. The home was visited in October 1955, and the following pets were investigated :
(i) Budgerigar in cage—negative ; (ii) Rabbit in garden—negative ; (iii) White mice in cage—negative ; (iv) Cat—positive for flea eggs on chair and rug by fire.
Instructions were given to dust the cat regularly with pyrethrum powder and to treat chairs and the cat's sleeping place. In spite of this the child still had attacks of urticaria papulosa. In March 1956, the cat was put to sleep with ether and yielded twenty-two female and eleven male cat fleas.
The child was free of spots for some months but later they appeared again. Further investigations showed that the child visited her grandmother regularly and sat on her knee with the grandmother's cat in a chair by the fire. A dust sample from this chair showed one adult cat flea, one larva and several flea egg shells. The grandmother's cat has been dusted regularly with pyrethrum powder and the child has remained free from spots.

The results of our investigations are shown in Table I.

TABLE I.

Number of cases.	Number in which parasites were found.	Species of parasites found.		Number in which parasites were not found.	Clinical improvement after control measures in the 27 cases where parasites were found.
40	27	Cat fleas,	20	13	19
		Hen fleas,	2		
		Pigeon flea,	1		
		House martin flea,	1		
		Human flea,	1		
		Undetermined flea,	1		
		Dog louse,	1		

We find that the human flea, *Pulex irritans*, is not a common cause of urticaria papulosa but believe it has been a probable cause in some cases which we have recorded as negative. We do not find the bed bug to be at all common, even in the poorest homes. Further investigation is needed to elucidate the

problem of why certain members of a family are affected whilst others are immune.

We believe that in time other infestations will come to be associated with specific eruptions as was suggested by Touraine (1947), e.g. a fine papular eruption may be connected with infestation by the dog louse.

Finally, we believe that papular urticaria is due to insect infestation in an allergic subject in the majority of cases.

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ULCERATING AND MUTILATING TROPHIC LESIONS OF THE LOWER LIMBS.

Y. BUREAU AND H. BARRIERE.
Nantes, France.

For several years we have been interested in certain patients presenting trophic lesions of the lower limbs accompanied by absorption of bone and disturbances of temperature sensation. These cases are not very rare for we have ourselves observed 27, and similar cases have been reported by various authors. The symptoms closely resemble those described by Thévenard as *Acropathies ulcéromutilantes*, but although our cases are related to those we consider that they are not the same because they are not familial and have certain other characteristic features.

In our group of cases there were 26 men and only 1 woman. It is essentially a disorder of adults ; the age of onset in our cases varied between 30 and 56 years, average 46 years. A case reported by Brodin *et al.* (1943) started at the age of 32. All our patients were of much the same type in that they were all poor, even destitute, and severely addicted to alcohol. Some were agricultural workers or small-holders, or humble fishermen ; the town dwellers were usually unskilled or semi-skilled workers or beggars, that is to say always people in humble cirstances living under difficult conditions and poorly nourished on a diet consisting mainly of soup and bread. This state of semi-starvation aggravated the alcoholism from which they all suffered.

In the second place we always found local contributory factors in the feet. In the most typical cases these were frost-bite of notable degree—exemplified by one of our patients who during the last war escaped from a prison camp and performed an extraordinary forced march of 800 kilometres in the snow ; he presented with perforating ulcers five years later. In other cases there was physical trauma either accidental or surgical, or even multiple small injuries resulting from walking in wooden *sabots* in conditions of non-existent hygiene. Further, we must emphasize that in our 27 cases the disorder affected only one member of the family as far as we were able to establish by questioning our patients. Finally we never found any other associated disorders or malformations in particular of the type of spina bifida.

Clinical Features

The lesions first appear on the foot which has been subject to trauma and it is only later that the other is affected. When the lesions affect both sides they predominate on the foot where local trauma has been more marked. There

are two types of lesions ; perforating ulcers, and a progressive deformity of the whole foot.

The perforating ulcers on the soles are very often the first manifestations of the disorder. Sometimes they begin with a transient bullous lesion which the patient takes for a traumatic blister ; alternatively, they develop as ulcers from the start. In either event it quickly acquires a characteristic appearance : There is deep ulceration, sharply outlined with punched-out edges, usually rounded but occasionally of irregular shape. The floor of the ulcer has a watery discharge sometimes slightly granulating and usually covered with a fairly thick, blackish crust. Occasionally this crust is greatly thickened and gives a warty appearance thus concealing the ulcer. A constant feature is that the ulcers are always completely indolent. Most often they are on the front of the foot especially under the big toe but they may appear also on the external margin of the foot and on the heel. It appears that at the onset of the disease these ulcers may occasionally heal spontaneously. Sometimes there are two or more.

The second type of lesion consists of a progressively developing deformity of the foot. It begins with a thickening of the toes which later spreads to the whole of the foot. In this way the foot becomes shortened and at the same time broader and thicker so that its general shape is almost cuboidal.

In addition to these changes, disturbances of sweating are always present giving rise to a striking appearance of the extremities, the skin becoming thin, moist, violaceous and succulent. We attach great importance to these signs of sympathetic disturbance which are rarely absent and which take the form of cyanosis and hyperidrosis of the extremities.

Disorders of sensation.—The lesions described above are accompanied by characteristic changes in sensation. The temperature sense is progressively blunted at first in the toes and later spreading proximally. Sensation of touch and pain persists or at the most may be partly blunted so that there results a dissociated sensory loss of the kind found in syringomyelia, which lasts throughout the whole course of the disorder ; but the distribution of the sensory change is not the same as that in syringomyelia.

These disturbances are always bilateral and fairly symmetrical ; we have never found them take up a distribution according to nerve roots and their upper limit always encircles the leg in the manner of a stocking. Deep sense always remains normal. Tendon reflexes are normal though occasionally the achilles reflex progressively disappears. Plantar reflexes are normal.

Bone lesions.—Bone lesions are always seen. The first change which is revealed by systematic radiological examination is in the terminal joints of the toes, as an arthritis of the interphalangeal or of the metatarso-phalangeal joints. At first a single joint may be affected in this way and when this is so it usually overlies the perforating ulcer. Later there is absorption of bone which may become very marked and lead to partial dislocation particularly of the inter-

phalangeal joints. This eventually leads to complete destruction of the joints of the toes and of the metatarsals. These changes of atrophy and bony rarefaction manifest themselves as a thinning of the bone ; the cortex appears paler and at the same time the outline of the bone becomes blurred and gives the metatarsals a very characteristic appearance. They are reduced to a triangular stump tapering at its distal end thus producing an extremely striking appearance which we have likened to a " partly sucked sugar-stick ". Eventually the whole of the bony cortex appears abnormally transparent.

Investigations.—The blood sugar is sometimes low but the tolerance curve is normal ; serum proteins are usually normal in spite of the poor nutritional state of the patients, though often globulin is raised leading to an A/G ratio which approaches unity. The serum cholesterol is often low with a low ester fraction. Above all, liver function tests (galactose tolerance, thymol, cephalin) give grossly abnormal results usually indicating liver damage which in two cases we confirmed by liver biopsy. This revealed lesions of variable severity, from milder changes with the liver cells having a clear cytoplasm with early fatty degeneration and a moderate localized cellular infiltrate, to more severe damage with well marked fatty degeneration, massive cellular infiltrate and a definite cirrhotic process which clinical and biochemical investigations had already indicated.

Serological tests for syphilis are negative. The cerebrospinal fluid is entirely normal.

Vascular circulation.—Oscillometry is always normal and indeed sometimes shows an augmented arterial circulation on the side which is most affected. Most of our patients do not have varicose veins. Arteriography of the small vessels of the legs shows arterio-venous communications producing tufts, the number of which is proportional to the severity and duration of ulcerated lesions. We consider these are secondary phenomena very comparable with those reported by Piulachs and Vidal-Barraquer (1953) and by Fontaine *et al.* (1954) as occurring in varicose ulceration, in post-phlebitic syndromes, and in leg ulcers following poliomyelitis. Their presence in these cases justifies the view which Fontaine expressed that these vascular channels are the consequence of sclerosis of the tissues.

Course.—The course is extremely chronic. It is, however, striking that the lesions remain exclusively localized to the lower limbs and in some of our patients which we have followed for more than ten years we have never seen any trouble in the arms. The disorder progresses extremely slowly, starting with perforating ulcers which heal with increasing difficulty. Then as the bony lesions become more marked the deformity develops and gives to the feet their characteristic appearance. From time to time the course is punctuated by attacks of inflammation affecting most often the toes but also the front part of the foot ; these lead to discharge of sequestra and may necessitate surgical

intervention which further increases the deformity. Dissociated sensory loss may extend a little above the knee in the most chronic cases but remains clear cut and we have never seen a complete loss of sensation.

Diagnosis.—The lesions we have described indicate a diagnosis of peripheral trophic changes of nervous origin. Within this category the combination of signs which our patients present enable us to exclude well recognized neurological disorders such as tabes. On the other hand, the clinical picture to some extent recalls that of leprosy and perhaps the pathogenesis lies somewhere between these two categories. One recalls some old descriptions of "lepra nostras", "indigenous leprosy" and even more so those cases of outcasts, destitute persons, survivors perhaps of an imperfectly assimilated racial group with trophic disorders which many authors ascribe to minor degrees of leprosy and correspond very well with the cases we now present. In fact, this type of social outcast seems particularly common in this part of the country.

We should emphasize that we have never found any clear manifestation of leprosy in these patients. These cases bear a close resemblance to the lesions of Morvan's disease, described as a feature of syringomyelia. The latter is indeed a diagnosis which comes first to the mind but the localization exclusively to the lower limbs, the absence of muscular atrophy, the distribution of sensory change and above all the course of the illness enables us to differentiate the two disorders.

There remains Thévenard's syndrome. The features which we have described are certainly very like those of Thévenard's (1942) syndrome but several authors have been struck by the points of distinction; thus de Sèze *et al.* (1944), distinguish between familial and non-familial cases, and Brodin *et al.* consider that the absence of familial or hereditary features in this disorder constitutes an important reason for distinguishing it. More recently Dereux (1952) has expressed the view that these patients present a separate nosological group which should be separated from Thévenard's syndrome (Table I).

TABLE I.

	Thévenard's syndrome.	Present Cases.
Family history	Very frequent	Constantly absent.
Sex	Indifferent	Predominantly men.
Onset	Childhood and adolescence	Middle age.
Site	Arms and legs	Exclusively legs.
Alcoholism	Inconstant	Very frequent.
Local factors	Not in evidence	Apparently necessary.
Signs of sympathetic involvement	Inconstant	Usual.

PATHOGENESIS.

It is still difficult to decide upon the pathogenic mechanism of these lesions for post-mortem examinations are rare. Taken together they confirm the absence of syringomyelia in the spinal cord and indicate on the other hand essentially peripheral lesions. All the reported cases are probably not strictly

comparable and some differ in greater or less degree. Only Barraquer-Bordas in the study of a familial case has recorded the existence of an intra-spinal cavity which was seen with the naked eye but was not studied histologically. Wadulla (1949) in a familial case described by Jughem and Krucke found various lesions which affected the spinal cord and at the same time the peripheral nerves, suggesting the possibility of a spina bifida lesion.

We would emphasize particularly that the studies that we know dealing with non-familial types (Girard *et al.*, 1956 ; Vignon *et al.*, 1956) confirm the absence of cord lesions and emphasize the occurrence of peripheral nerve lesions of degenerative type affecting the posterior roots and the sciatic nerve trunk.

Nerve Lesions.

We have not had any autopsy among our patients but we have been able to study the sympathetic system in several cases where sympathectomy was carried out. In this way we have been able to observe several lesions :

Hyperplasia and vascular congestion.—Vascular hyperplasia and congestion often occurs, the vessels being engorged and surrounded in one case by a cuff of marked oedema and in another by a perivascular infiltrate with polynuclears.

Cellular pyknosis and chromatolysis.—Cellular involvement is revealed by a change in the appearance of the cytoplasm which shrinks and becomes basophil while the nucleus becomes dense and takes up an eccentric position. These changes lead on finally to pyknosis.

Pigmentation.—While bearing in mind the increase in pigmentation which takes place with age, we were struck by the abundance of pigment granules in our cases, particularly since our patients were relatively young—one aged 31 and three others between 44 and 50.

Satellitosis.—There is an increase in number of the round cells which form the envelope to each nerve cell. This lesion is called " satellitosis " by Ivan Bertrand.

Fibrosis and gliosis.—There is a reaction of fibrosis which results in thickening of the septa within the ganglia and of the perineural sheaths which surround the nerve filaments. The degree of fibrosis is variable and does not seem to be directly proportional to the duration of the disease. In one case it was of mild degree in a man aged 63 who had been affected for about 15 years. We could find no telangiectatic granuloma of the stroma nor vascular hyaline change, nor amyloid or hyaline infiltration of the interstitial tissues.

We could not trace a definite sequence in the development of these lesions. Perhaps the vascular changes come first, to be followed by cellular infiltrates and eventually fibrosis of a degree which varies from one case to another. It is evident that none of these lesions are specific but they acquire considerable significance when they occur together. They are comparable with those re-

ported by van Bogaert (1953) in a specimen removed at sympathectomy in a patient with peripheral trophic lesions which followed five years after frost-bite. The sympathetic ganglia showed an increase in number and diameter of venules with a thickening of the glial septa.

Thus, although more or less nonspecific, the lesions in the sympathetic ganglia of our patients seem to be worthy of attention because we have found them so constantly ; we think that they must play a part in the production of the disorder. We think it possible thus to propose the following pathogenesis : First, lesions of the extremities either of single considerable trauma or repeated small injuries bring about an alteration in the terminal branches of the venous network in particular in the skin and hypoderm. Second, the malnutrition resulting from alcoholism and a dietary insufficiency produce metabolic changes which favour the spread of lesions and thus allow the progressive development of the disorder. One may then postulate either an ascending neuritis (Guillain and Dubois, 1914) or preferably a sympathetic nerve reflex. The constant presence of clinical signs of sympathetic disorder and the benefits obtained by sympathectomy favour the latter hypothesis.

Treatment.

Experience has shown that lumbar sympathectomy should be carried out early if good results are to be obtained. In later cases where vascular shunts are already discernible by arteriography, improvement obtained is incomplete and temporary.

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ROYAL SOCIETY OF MEDICINE

SECTION OF DERMATOLOGY.

President.—Dr. John T. Ingram.

20 February 1958.

Hyperpigmentation of Hair following Chloroquin.—Dr. Stephen Gold.

History.—A woman aged seventy-two first developed lupus erythematosus in May 1955, with an eruption confined to the nose, cheeks and neck. Treatment with mepacrine cleared the eruption after about four months. In the following year, in spite of simple precautions, there was a recurrence following exposure to sun. Chloroquin was prescribed, 300 mg. daily, starting on 5 June 1956, and she continued on this dose for six weeks with good effect. In November 1956, there was a renewed phase of activity, and chloroquin was again administered. An episode of acute thrombophlebitis of the right leg necessitated admission to hospital in January 1957 and throughout this period she was maintained on chloroquin 400 mg. daily until February 1957. In April, it was noticed that the lupus erythematosus was much improved, but there had developed a yellow-stained forelock, quite noticeable when compared with the general greyness of her hair and resembling nicotine staining. Chloroquin was reduced from 400 mg. to 200 mg. daily. By the end of May 1957, the lupus erythematosus had completely cleared and the yellow forelock appeared to be growing out. At this time chloroquin was stopped. Through June and July 1957, the L.E. remained inactive, but for one period of three weeks in July she took chloroquin 200 mg. daily. By November 1957, it was noted that she was virtually free of active L.E., and the yellow forelock had practically grown out. There was some hypopigmentation in her lashes and brows, but more striking were the symmetrical areas of increased pigment in the hair at the sides of her scalp and to a less degree at the back. This was something quite new and was remarked upon by all members of her family.

Examination.—The darkened hair at the sides is apparent, although the lupus erythematosus is virtually imperceptible.

Poikiloderma Congenitale (Thomson).—Dr. Stephen Gold.

History.—A girl aged eleven, born with a deformed right foot and leg ; there was also a coloboma of the right eye with internal strabismus, for which three operations have been performed. As well, there has been crowding of the teeth with notching of the edges of both upper and lower incisors. There is congenital absence of a clavicle and shortness of the neck of the right femur. The right foot is the same size as the left, but at birth there were only four toes, the lateral two representing the third, fourth, and fifth digits ; there was marked lateral deviation of the foot. There was also some degree of microcephaly, and later her I.Q. was judged to be sub-standard. Shortly after birth, a large papilloma was removed from her lower lip and it was then noticed that there was some notching of the right ala nasi. Orthopaedic treatment has resulted in some improvement of function of the foot and she is now able to walk normally with some degree of inversion.

There is no family history of ectodermal defect, but it is significant that during pregnancy the patient's mother contracted infective hepatitis as well as influenza. The child herself is said to have had rubella at an early age.

Examination.—There is some cribriform atrophy of the cheeks with telangiectasia. On the trunk there are three or four large atrophic pale areas representing ectodermal defects. Both legs show streaky telangiectasia with some overlying hyperkeratosis.

This patient was shown at the International Congress in London, 1952, by Dr. H. T. H. Wilson. Case No. 105.

Discussion.

Dr. D. I. Williams: This was not quite the type of case which Sydney Thomson originally described. His case and some others we have since seen here have a curious orange colour, they do not scar like this, they produce warty lesions and they have bony defects; although this is not the classic picture described 23 years ago it must be very close to it.

Dr. A. J. Rook: I believe that a sufficiently large number of cases of the Rothmund-Thomson syndrome has now been described to allow a reasonably precise definition of the limits of a very distinctive syndrome. The age and mode of onset of the skin lesions, their distribution and the frequent presence of light sensitivity are characteristic features. This patient presents a most interesting combined mesodermal and ectodermal developmental defect but I think that there is a good case for excluding it from the Thomson syndrome. Some of the associated abnormalities present here are, after all, common to many genodermatoses.

Linear Atrophy.—Dr. Mary Witham (for Dr. W. N. Goldsmith).

A girl aged 13 years.

History.—At 3 years of age she developed a capillary haemangioma of linear distribution on the medial aspect of the left thigh and lower leg. This faded after treatment with thorium-X paintings 2,000 ESU/ml. on 12 occasions at 3 week intervals (Dr. Martin-Scott).

Six months after completing treatment, the skin on the treated area became dry and began to "sink in" until a depression developed in the site of the original angioma.

Since then there has been a noticeable difference in the diameter of the limbs but the leg has grown normally in length and there has been no weakness. She swims and rides with no difficulty.

Examination.—There is a deep depression extending from the left iliac crest to the postero-medial aspect of the knee. The skin is not thickened and veins are readily seen in the floor of the groove. There is loss of subcutaneous fat on the medial aspect of the left lower leg. The left calf and thigh are half an inch less in diameter than the normal limb. The affected limb shows no shortening. Muscle power is good and equal on both sides. Reflexes are normal. There is no sensory loss. Over the sacral region there is a fine growth of hair.

Investigations.—Skiagram of lumbar spine: posterior processes of S.1. have not fused and those of L.5 are rather small. Skiagrams of both legs: loss of subcutaneous fat in region of left thigh and calf. The muscle mass is about the same size on both sides. There is a little subcutaneous calcification on the medial aspect of the affected leg about three inches above the ankle joint.

Biopsy: Slight thinning of the epidermis. The collagen is somewhat more condensed than normal but it is not frankly sclerodermatous. The appendages are still present. Any changes in the skin resembling scleroderma are minimal.

Comment.—Rubin (1948) described 13 cases of linear scleroderma of segmental distribution, of which 70% had spina bifida occulta. Histological examination was carried out in only half the cases and full clinical descriptions are not given. It is therefore possible that some of them were similar to this girl.

It is suggested that this atrophy of subcutaneous fat is developmental in origin and its association with a capillary haemangioma and with spina bifida occulta is of interest. We do not consider that the treatment with thorium-X caused the condition and it may not have been responsible for banishing the haemangioma.

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Discussion.

Dr. R. T. Brain : I am reminded of the cases which I have described and shown here under the title of "naevus vascularis reticularis". The condition appears to be a mesodermal defect involving the venous system and associated with varying degrees of atrophy of the skin. In this case larger vessels are involved and the process extends more deeply. I am uncertain about the nature of this unusual lesion.

Scleroderma (Acrosclerosis Type).—Dr. W. N. Goldsmith.

A man aged 49, a printer.

History.—August 1944, foreign body from flying bomb entered left forearm, two inches above the wrist. There has been numbness of left thumb ever since. Dysphagia and "indigestion" began at about the time of this injury. The "indigestion" consists of a pain in the throat, 3–4 hours after meals, and which wakes him at night. It is relieved by sitting up, and by alkalies.

1949, swelling of fingers started on the left hand, and very soon appeared on the right hand as well. Finger-tips became warty and tender. The warty growths were easily knocked off, leaving small necrotic ulcers.

1950, Raynaud-like symptoms began. They are worse in cold weather, but occur in summer also. No exposure to severe cold or vibration.

1953, occasional bouts of diarrhoea.

Smokes 20 cigarettes a day. Weight 8 st. 12 lbs. Used to be 11 st. Has lost weight because dysphagia causes him to eat the minimum amount of food.

Examination.—Fingers swollen and skin taut and smooth. Index fingers shortened. Tips of several are ulcerated. Slow return of colour after pressure. No evidence of arteriosclerosis. Fundi normal. B.P. 158/86. No other abnormality.

Investigations.—Urine creatinine 1·1 g. in 24 hours. Urine creatine 0·095 g. in 24 hours (normal 0·0–0·06 g./24 hours). Hb% 110, W.B.C. 4400, with normal differential, ESR 11 mm. in 1 hour, WR and Kahn negative, cold agglutinins negative, electrophoretic strip (serum proteins) normal, alk. phosphatase 12·9 units 100 ml.

E.C.G.: No evidence of cardiac involvement.

X-ray Examinations : Lung fields clear, no cervical ribs.

Barium Swallow : Narrowing of the lower three inches of the oesophagus. Free reflux seen in supine position. Mucosal folds in lower part of oesophagus are a little thickened, but intact. Diagnosis: Reflux oesophagitis with early stricture.

Fingers : Gross loss of bone in distal portions of many digits. Some generalised osteoporosis. Some periosteal reaction.

Balloon Studies (Dr. D. A. W. Edwards) : A peristaltic wave was found to be initiated by the cricopharyngeus muscle, but proceeded only 4 cm. down the gullet. The rest of the oesophagus showed no peristaltic activity. These changes are characteristic of scleroderma.

Biopsy : A portion of skin from one of the fingers showed moderate apparent homogenisation of collagen.

Comment.—This type of scleroderma is rare in men. Moderate Raynaud-like symptoms did not begin till six years after the dysphagia and one year after the swelling of fingers. Otherwise there is no evidence of cardio-vascular disease. If the disorder were primarily vascular, it would be difficult to explain why just the fingers and oesophagus should be involved.

A neurotrophic origin is easier to reconcile with the facts. The illness started just after a severe shock. The same contiguous strip of spinal cord serves both the oesophagus and the fingers and some degree of improvement in early cases has been claimed from sympathectomy, both of the digital and of the oesophageal affections. Band-like scleroderma of the lower limbs is often associated with spina bifida. I might also remind members of Haxthausen's (1947–48) transplantation experiments and the work of Ormea (1952) and Gebauer and Halter (1947).

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Discussion.

Dr. F. Ray Bettley : This case draws attention to the oesophageal changes caused by what in the first place is possibly nothing more than a cessation of peristalsis, then reflux, leading to oesophageal ulceration followed by sclerosis. These patients may then get into a very difficult position when they have a severe oesophageal stenosis which it may be extremely difficult to remedy.

I saw a case of this sort about three years ago and it became necessary to excise this oesophageal stricture, an operation of the greatest difficulty because the oesophagus above it had practically no muscle—there was not much more than mucous membrane with a little submucous tissue. The man survived because the surgeon brought the stomach up into the chest to make up the defect but I am sure that it was an extremely difficult operation and the patient might well have died.

Dr. R. D. Sweet : Has any member treated any of these patients with this difficulty in swallowing with a course of prednisone ? We had a patient who got to the stage where she could not swallow at all. She was put on prednisone and did very well indeed, presumably because of the reduction of the inflammation.

Dr. Maurice Garretts : One point about steroid therapy in the patients with reflux is that it increases the acid secretion of the stomach and that would increase the ulceration at the lower end of the oesophagus.

Dr. G. B. Dowling : On the question of treating this kind of scleroderma with steroids, I am inclined to think that there is a definite risk. I have seen three cases, two under my care, who had quite a short course of steroids, about six weeks or so without a very great deal of improvement—some loosening up of the fingers. Some months later, each of these patients died of uraemia. A third case was treated in that way, became very ill and was admitted under my care. She died also of uraemia. There have been other cases published which suggest that this treatment may accelerate vascular scleroderma or may even initiate it. There is enough I think in the literature and in my own cases to make one think very hard before using steroids in this condition.

Porokeratosis of Mibelli with Squamous Cell Carcinoma.—Dr. E. N. M. Johnston (for Dr. O. L. S. Scott).

A man aged 50.

History.—At the age of 9, a blemish was noted on the left ankle. During the past 41 years, further lesions have appeared, spreading up the left lower limb and now involving the left side of the trunk and left upper limb. During the past year, early lesions have appeared on the right forearm. Two years ago, a swelling appeared on the back of the left leg and has slowly enlarged.

Family History.—No similar skin condition. No consanguinity of parents.

Examination.—Healthy man with no abnormal physical signs apart from the skin lesions. A peculiar systematized naevoid type of lesion is present on the above named sites. Lesions are present also on the left side of the glans penis. The distribution is linear and the lesions consist of rough flat pigmented macules with atrophy in some areas and hyperkeratosis in others. Some lesions show a fine thread-like edge. A fleshy tumour is present on the back of the left leg. There is no significant regional lymphadenopathy.

Investigation.—Histology of biopsies : 1. From macular lesion of back of left thigh : The changes of porokeratosis are present. 2. From the tumour of the left calf. The characteristics of squamous cell carcinoma are present.

Discussion.

Dr. Peter Smith : In Minneapolis in 1950 I saw an identical case being treated for a squamous-cell epithelioma in the x-ray department.

Acne Agminata, Granuloma Annulare.—Dr. J. H. Allison (for Dr. F. Ray Bettley).

A woman aged 42.

History.—For the last 3 years she has had crops of papules on the cheeks, nose, forehead, and the dorsa of the hands. The papules on the face last for 2 or 3 weeks and then clear spontaneously, leaving a depressed scar. The papules on the dorsa of the hands and wrists tend to last 4 to 5 weeks and then clear spontaneously. Apart from these skin lesions, she is quite fit.

Examination at various times over the last 18 months has shown flat red papules on the backs of the hands and wrists, suggestive of granuloma annulare. Following the withdrawal of blood from a vein in the right antecubital fossa, a similar papule appeared and gradually spread to form an annular lesion typical of granuloma annulare.

She has never been entirely free of papules on the face, usually having 1 or 2 lesions consisting of brownish-pink papules.

Investigations.—Mantoux Heaf test positive, chest x-ray normal, blood count and sedimentation rate normal, x-ray of the hands normal. Plasma protein 7·6 g.% (Albumin 4·9 g.%, Globulin 2·7 g.%), electrophoretic pattern normal.

Histologically, the lesions on the hands and the right elbow are typical of granuloma annulare, showing necrotic collagen surrounded by a pallisade of epithelioid cells, lymphocytes and occasional giant cells. The lesions on the face show an area of necrotic collagen with a surrounding infiltrate of epithelioid cells and giant cells arranged in follicles.

Comment.—If it is agreed that this patient has in fact both granuloma annulare and acne agminata, then the closely parallel course of the two conditions combined with the several similarities in the histology suggest that there may be a common mechanism of production of the two types of lesion.

Discussion.

Dr. C. D. Calnan : A number of cases of granuloma annulare arise during the treatment of tuberculosis of the skin with calciferol and with INH.

Dr. F. Ray Bettley : I am very much inclined to the view that although these are called tuberculides they may have nothing to do with the tubercle bacillus. Our predecessors went through the same stage with granuloma annulare. In fact, it is now well recognized that a tuberculoid histology may be produced by a great variety of agents. I believe that this patient presents not two separate diseases, acne agminata and granuloma annulare, but more probably one disorder which produces lesions sometimes suggesting one of those, sometimes the other. It perhaps indicates that those two diseases are not as clearly distinct entities as is usually thought.

Dr. Henry Haber : The lesions of the face show tuberculous granulomata with central necrosis. The lesions of the body show central necrosis of the collagen surrounded by a typical inflammatory reaction. I think the patient has acne agminata of the face and granuloma annulare elsewhere. We have seen cases of lupus vulgaris developing granuloma annulare whilst on treatment with calciferol.

The following cases have been published in *Proc. R. Soc. Med.* **51**, 517 :

Kaposi's Varicelliform Eruption Treated with Prednisone.—Dr. S. C. Gold.
Multiple Skin Necroses (Arteriolar).—Dr. Maurice Garretts.
Pretibial Myxoedema.—Dr. K. M. Harvey (for Dr. Brian F. Russell).

The following cases also were shown :

Rosacea Treated with Intermittent "Vallestril" Therapy.—Dr. A. Jarrett.
Post-thrombotic Ulceration of the Toes.—Dr. Maurice Garretts.
Lupus Vulgaris with Erupting Cysts.—Dr. D. S. Wilkinson.
Onchocerciasis.—Dr. B. Schwartz.
Eosinophilic Granuloma.—Dr. J. Savage.

CURRENT LITERATURE.

THE EVALUATION OF VARIOUS ANTIHISTAMINES AS LOCAL ANAESTHETIC AGENTS. C. G. Steffen, R. Mihan and M. Zimmerman. [1957] *J. invest. Derm.*, **29**, 7.

For the purpose of minor operations on the skin, surgeons were supplied with pyribenzamine benadryl neo-antergan chlortrimetron and normal saline in place of their usual local anaesthetic, and were invited to comment on their efficiency.

Save in the case of normal saline which was quite ineffective there were few complaints and the conclusion is reached that 1% pyribenzamine would be an excellent substitute for procaine in patients allergic or refractory to that drug. J. H. T. D.

INHIBITION OF INTRACUTANEOUS LEISHMANIN REACTION BY HYDROCORTISONE ACETATE. A. Dostrovsky and A. A. Cohen. (1957) *J. invest. Derm.*, **29**, 15.

The leishmanin reaction, which is of the delayed tuberculin type, is a stable and fairly prolonged affair and it is highly specific.

Systemic cortisone and ACTH only very slightly modify the reaction. Leishmanin and hydrocortisone injected together—no reaction. Leishmanin together with cortisone or ACTH with or without hyaluronidase—reaction unaffected. The course of a developed leishmanin reaction is shortened and suppressed by the local injection of hydrocortisone, the earlier the more. Although hydrocortisone may persist in the tissues a positive leishmanin test becomes possible again after a fortnight. J. H. T. D.

TRICHOPHYTON EQUINUM—A RE-EVALUATION OF ITS TAXONOMIC STATUS. L. K. Georg, W. Kaplan and L. B. Camp. (1957) *J. invest. Derm.*, **29**, 27.

T. equinum has of course been isolated from cases of human ringworm; but it will not grow *in vitro* on horse, mule or donkey hairs unless nicotinic acid is supplied.

Thirty-three strains of *T. equinum* obtained from various sources displayed this specific requirement, which is not shared by other dermatophytes. J. H. T. D.

MELANOTIC WHITLOW (SUBUNGUAL MELANOMA). S. H. Gibson, H. Montgomery, L. B. Woolner and L. A. Brunsting. (1957) *J. invest. Derm.*, **29**, 119.

A review of 52 cases of melanotic whitlow reported in the literature and an analysis of 38 cases encountered at the Mayo Clinic disclosed the following.

Melanotic whitlow probably represents some 3% or 4% of all melanomas. Approximately 80% of the patients are about equally distributed among the fifth, sixth and seventh decades of life. Patients with this form of melanoma are older than patients with other forms of melanoma. There is no significant difference in incidence between the sexes. The lesion most frequently involves the upper extremity, especially the left thumb; two-thirds of the lesions involve either a thumb or a great toe. Although of questionable significance, trauma is associated with more than 40% of the cases and as frequently in one sex as in the other. The initial lesion is either inflammatory or pigmented. Only one-eighth of the lesions are painful. Gross pigment may be found in more than half of the cases. In two-thirds of the cases some form of minor surgical procedure has been carried out before the diagnosis is suspected. In only half of the cases is the diagnosis made within the first 2 years of onset. In at least one-third of the cases obvious metastasis has occurred by the time the diagnosis is made. The chief complaint of all 38 Mayo Clinic patients was related to the chronic and inflammatory nature of their lesions. Seventeen patients were aware of the malignant nature of the whitlow at the time of admission. Absence of discernible metastasis at the time of operation does not necessarily imply a better prognosis. Except for absence of involved regional nodes at the time of diagnosis and treatment, nine "cured" patients did not differ in any significant manner, clinically or histologically, from those of the whole group.

Study of tissue from 33 of the 38 Mayo Clinic cases disclosed no practical criteria for grading malignancy or predicting outcome in individual cases. Practically all the lesions were invasive and mitotically active. On the basis of failure to demonstrate pigment in sections stained with haematoxylin and eosin and with silver nitrate 6 cases were classified as amelanotic melanoma. Origin of the tumour from the nail bed was demonstrated in 25 of the 33 lesions.

Of the 38 Mayo Clinic patients, 19 died of melanoma, 3 of these having survived longer than 5 years after operation, 6 died of other causes, 1 has been lost to observation and 12 patients are still living. Six of the 12 living patients are not yet postoperative for a 5-year period, and 3 of the these are known to have metastases. No conclusions regarding treatment, survival rates or prognosis are drawn from this study. J. H. T. D.

ALLERGIC SENSITIZATION TO ADHESIVE TAPE. EXPERIMENTAL STUDY WITH A HYPOALLERGENIC ADHESIVE TAPE. E. Sidi and M. Hincky. (1957) *J. invest. Derm.*, **29**, 81.

A discussive and fanciful exploration of the possibilities of allergy to the various forms of zinc oxide plaster. The properties of a new adhesive are described and the formula disclosed. J. H. T. D.

RATIONALE FOR THE TREATMENT OF LUPUS ERYTHEMATOSUS WITH ANTIMALARIALS. E. W. McChesney, F. C. Nachod and M. L. Tainter. (1957) *J. invest. Derm.*, **29**, 97.

The authors bring support to the view that the therapeutic value depends on a sunscreening action. They recommend treatment with a mixture of chloroquine and hydroxychloroquin, of each 2 parts and quinacrin one part. J. H. T. D.

RESULTS OF PATCH TESTING WITH RUBBER ANTIOXIDANTS AND ACCELERATORS. L. E. Gaul. (1957) *J. invest. Derm.*, **29**, 105.

In view of the practical difficulties in obtaining materials for patch-testing patients allergic to articles of footwear and of ascertaining their nature, the author uses a routine series of patch tests with (1) monobenzyl ether of hydroquinone, (2) phenyl beta naphthylamine, (3) mercaptobenzothiazole, (4) tetramethylthiuram monosulphide and (5) diphenylguanidine. J. H. T. D.

STUDIES ON VASCULAR SKIN RESPONSES IN ATOPIC DERMATITIS. THE INFLUENCE OF PSYCHOLOGICAL FACTORS. F. Kalz, E. D. Wittkower, G. W. Vavruska, P. Telner and S. Ferguson. (1957) *J. invest. Derm.*, **29**, 67.

A rough psychiatric classification of patients with flexural prurigo would divide them into the extroverted and the introverted. The former give a normal response to intradermal histamine; in the latter the flare fails to appear; but in both the reaction may change under the influence of psychiatric treatment or adventitious emotional stimulus.

This interesting paper contains a full discussion of the relevant applied physiology including the evidence that the altered reaction is independent of the nerve supply. J. H. T. D.

AN ELECTRON MICROSCOPE STUDY OF THIN SECTIONS OF HUMAN SKIN. II. SUPERFICIAL CELL LAYERS OF FOOTPAD EPIDERMIS. C. C. Selby. (1957) *J. invest. Derm.*, **29**, 131.

The tonofibrils and intercellular bridges of the rete appear in this study to represent a fibrous keratin precursor which in the stratum granulosum changes into the keratin of the horny layer, the larger and more irregular granules of keratohyalin representing a by-product.

(The electron microphotographs illustrating this paper may be thought to demonstrate that even the inconceivably small can be made recognizable in structure and function by sufficient magnification.) J. H. T. D.

RAPID CLASSIFICATION OF CANDIDA (MONILIA) ALBICANS. W. J. Fahlberg, C. D. Dukes and R. K. Guthrie. (1957) *J. invest. Derm.*, **29**, 111.

Incubated on human-blood agar plates at 37° C. for 48 hours in an atmosphere containing 6–8% CO_2, *Candida albicans tropicalis* and *stellatoidea* each produce colonies differing sufficiently in appearance to make recognition possible. That of *albicans* has a characteristic fringe. J. H. T. D.

HISTOLOGY AND CYTOCHEMISTRY OF HUMAN SKIN. XII. CHOLINESTERASES IN THE HAIR FOLLICLES OF THE SCALP. W. Montagna and R. A. Ellis. (1957) *J. invest. Derm.*, **29**, 151.

It has been supposed that specific cholinesterases are peculiar to the postganglionic fibres of the parasympathetic nervous system, but their presence in the sensory nerve plexus surrounding the hair follicle is here demonstrated by a reaction with acetylthiocholine iodide that can be abolished by treatment of the material with physostigmine. J. H. T. D.

MELANOCYTE COUNTS ON HUMAN FOREARM SKIN. A. S. Breathnach. (1957) *J. invest. Derm.*, **29**, 181.

The author's material, obtained in all 10 cases from the proximal part of the medial aspect of the forearm of healthy white males, yielded higher counts (1750 to 2325) than those of other investigators. J. H. T. D.

IN VITRO INVASION OF HAIR BY DERMATOPHYTES. F. Raubitschek. (1957) *J. invest. Derm.*, **29**, 161.

The attempt to produce *in vitro* invasion of the hair shaft by the continuous shaking culture technique was successful in hair obtained from only one of 4 young girls. J. H. T. D.

PRIMARY IRRITANT ACTIVITY OF BARRIER CREAMS. J. Tas. (1957) *J. invest. Derm.*, **29**, 223.

Forty-eight-hour patch tests were performed on 300 subjects, mostly suffering from eczema, with 6 different barrier creams and with 13 other materials including nickel, chrome, procaine, paraphenylene diamine and turpentine. The barrier creams provided most of the positive reactions : one oil-resistant type in 50% of the subjects tested. The author points out that the patch test involves a more severe exposure than the usual protective inunction (or even the exposures involved in manufacture !) and urges that in spite of their irritant character, now revealed, they have been used with great success in the prevention of industrial dermatoses. He fails however to reach the conclusion that, in view of the possibility that they may well play the same role in prevention as the placebo does in therapy, they could with advantage be compounded of simpler and non-irritating constituents. J. H. T. D.

CADMIUM SULPHIDE SUSPENSION IN SEBORRHOEA CAPITIS. W. L. Kirby. (1957) *J. invest. Derm.*, **29**, 159.

Successful in 79 out of 84 cases of seborrhoea capitis ; and no mishap. J. H. T. D.

PERIODIC ACID-SCHIFF POSITIVE MATERIAL ACCUMULATING WITHIN THE LUMEN OF ECCRINE SWEAT GLANDS. G. W. Hambrick. (1957) *J. invest. Derm.*, **29**, 213.

In the course of an experiment in which part of the skin of the back was treated with chlorinated naphthalene and another part, as a control, with acetone or naphthalene in acetone, there was noticed in sections of both areas in two negro subjects periodic acid-Schiff positive material in the lumina of eccrine ducts. J. H. T. D.

DETECTION OF RADIATION EFFECTS ON HAIR ROOTS OF THE HUMAN SCALP. E. J. Van Scott and R. P. Reinertson. (1957) *J. invest. Derm.*, **29**, 205.

An account of the effect, on the hair bulb and keratogenous zone of hairs in the anagen phase, of exposure of the scalp to x-rays and to electrons emitted from a Van de Graaff generator. J. H. T. D.

THE GROWING HAIR ROOTS OF THE HUMAN SCALP AND MORPHOLOGIC CHANGES THEREIN FOLLOWING AMETHOPTERIN THERAPY. E. J. Van Scott, R. P. Reinertson and R. Steinmuller. (1957) *J. invest. Derm.*, **29**, 197.

In tufts of about 50 hairs plucked from normal scalps by means of a surgical needle holder, round about 85% are found to be in the anagen phase. The percentages in hair plucked from patients with malignant disease including leukaemia varied between 24 and 90 and differed from one time to another. Two weeks after an intravenous dose of amethopterin a sharp constriction could be seen in a high proportion of anagen hairs corresponding to an inhibition by the drug of mitosis in the hair bulb. J. H. T. D.

SEBORRHOEIC KERATOSES. I. " PSEUDO-EPITHELIOMATOUS HYPERPLASIA " (WEIDMAN). Lyon Rowe. (1957) *J. invest. Derm.*, **29**, 165.

Describes some difficulties in the clinical and histological diagnosis of seborrhoeic keratoses, in particular that of avoiding the diagnosis of squamous carcinoma arising out of one. (We might rather wish that he had explained to us why these wart-like structures, presumably either naevoid or neoplastic, are called " seborrhoeic ".) J. H. T. D.

MELANOCYTE DISTRIBUTION IN FOREARM EPIDERMIS OF FRECKLED HUMAN SUBJECTS. A. S. Breathnach. (1957) *J. invest. Derm.*, **29**, 253.

Actually there are little more than half as many melanocytes, at any rate dopa-positive ones, in the freckles than in the surrounding skin. It will be necessary to study the epidermis of likely-to-be-freckled children under 2 years old in order to ascertain if this unequal distribution is congenital or acquired. J. H. T. D.

QUALITATIVE AND QUANTITATIVE DATA ON MELANOCYTES IN HUMAN EPIDERMIS TREATED WITH THORIUM X. R. J. Staricco. (1957) *J. invest. Derm.*, **29**, 185.

In skin reacting mildly to thorium X the melanocytes exhibit increased activity, send out long processes, and may even ascend the outer layer and be desquamated, but they do not increase numerically out of proportion to the basal cells. J. H. T. D.

THE DERMATOLOGIST AS AN INDIVIDUAL—AN APPRAISAL OF CULTURAL TRENDS. M. E. Obermayer. (1957) *J. invest. Derm.*, **29**, 241.

The President reminds us that medicine was once a learned profession. He also deplores the tendency for the dermatologist to become little more than a distributor of pharmaceuticals, applying the facts and pseudofacts handed out to him by the biochemists, microbiologists and physicists to the needs of the patients. (But it is not altogether clear what could be the value of a cultural background in dealing with the people who to-day constitute the majority of our patients even apart from the cost of maintaining it in relation to material rewards.) J. H. T. D.

EXAMINATION OF THE EPIDERMIS BY THE STRIP METHOD. IV. THE MELANOCYTES DURING A PERIOD OF FORCED REGENERATION. P. J. Kropp. (1957) *J. invest. Derm.*, **29**, 217.

While stripping provokes an outburst of mitotic activity in the basal layer it has little or no effect, in contrast with that of thorium X, on the melanocytes. J. H. T. D.

COMPARATIVE STUDIES OF SPECIAL MEDIA FOR IDENTIFYING CANDIDA ALBICANS FROM OTHER CANDIDAS AND MOLDS. Bahram Sina and F. Reiss. (1957) *J. invest. Derm.*, **29**, 263.

No species of *Candida* other than *albicans* produced chlamydospores on either rice infusion agar, cornmeal agar or Bacto-chlamydospore agar. Chlamydospores appeared on rice infusion agar in all of the 30 cases examined but failed 7 times in each of the other two media. J. H. T. D.

DETERMINATIONS OF SQUALENE IN SEBUM FROM THE FOREHEAD OF PATIENTS WITH SKIN CANCER. H. Sobel, J. Marmorston, E. T. Wright and E. Garcia. (1957) *J. invest. Derm.*, **29**, 264.

Squalene is supposed to neutralize the carcinogenic properties of methylcholanthrene. The normal secretion from the forehead is 1·4–7·3 mg. per sq. cm. averaging 5·11 ($\pm$ 0·36) in 22 subjects. Eighteen patients with basal-celled growths averaged 10·58 ($\pm$ 1·02) provided you leave out the 3 noncomformists who averaged 3·2; while the 12 with squamous growths averaged only 2·86 ($\pm$ 0·28) if we agree to overlook three at 6·8, 8·2 and 10·4. J. H. T. D.

SIMPLE TESTS FOR THE DEMONSTRATION OF THE LOW FREE AMINO NITROGEN CONTENT IN PSORIATIC SCALES. P. Flesch and E. C. Jackson Esoda. (1957) *J. invest. Derm.*, **29**, 247.

If you want to distinguish between "normal and pathologic scales" you can chromatograph a drop of watery extract with a phenol water mixture and develop it with ninhydrin. While psoriatic extracts show very faint spots or none at all, extracts of callus develop a "marked pattern". J. H. T. D.

THE INHIBITION OF PERSPIRATION BY MEANS OF THE TOPICAL APPLICATION OF MALONIC ACID SALTS. A. Rostenberg and E. J. Gonzalez. (1957) *J. invest. Derm.*, **29**, 251.

Since malonate ions competitively inhibit the enzyme succinic acid dehyrogenase, which has been shown to play some part in eccrine sweating, it was not unreasonable to try a 20% sodium

malonate ointment. And it seems to work at least as well as various commercial antiperspirants containing alum but the performance of none of them was encouraging at 100° F. and 20% relative humidity. J. H. T. D.

FOCAL HEPATITIS, FEVER AND SKIN RASH FOLLOWING THERAPY WITH SULFAMETHOXYPYRIDAZINE, A LONG-ACTING SULPHONAMIDE. W. A. Tisdale. (1958) *New Engl. J. Med.*, **258**, 687.

A generalized maculo-papular eruption with petechiae in the mouth, leucopenia, fever and hepatitis developed in an elderly man after a course of sulfamethoxypyridazine given for infection of the urine. Apparently only fever and eruption on the skin had been noted previously to follow the use of this drug. In spite of negative patch tests and intracutaneous tests the signs in this patient were attributed to an allergic response to the drug. A. D. P.

BENIGN MUCOUS MEMBRANE PEMPHIGUS. P. L. McCarthy and G. Shklar. (1958) *New Engl. J. Med.*, **258**, 726.

Fifteen cases of benign mucous membrane pemphigoid are reviewed in this article.

The authors noted that scarring rarely followed bullae within the mouth and that pain was generally a constant symptom.

Corticosteroids were used exclusively for treatment, though only seldom was it possible to suppress all signs of disease. A small maintenance dose was usually given, unless eye lesions were advancing. A. D. P.

RUBBER AND ECZEMA (1st communication). E. Schultheiss. (1958) *Berufsdermatosen*, **6**, 49.

The term rubber dermatitis is used to cover all cases encountered in the rubber industry, both natural and synthetic, and through contact with manufactured goods containing rubber.

In conjunction with works medical officers and managements of large rubber factories the author has designed two test series to investigate suspected cases of which full details are given. There is a list of articles containing rubber that have caused sensitization and have been mentioned in the literature. Sensitization is caused not by the natural rubber but by substances used in manufacturing processes. All chemicals known to be sensitizers are listed. Special reference is made to hydroquinone-monobenzylether causing depigmentation, chloronaphthalene producing chlor-acne and zinc oxide acne. Reversible alopecias due to chloroprene used in the manufacture of synthetic rubber are mentioned.

Further information on rubber technology, case records and evaluation of skin tests will be given in a subsequent paper. One hundred and sixty-two references are given.

W. G. T.

THE CLINICAL TESTING OF A SOLID SYNTHETIC WASHING AGENT. A. Greither and H. Greither. (1958) *Berufsdermatosen*, **6**, 70.

The popular prejudice against liquid soaps which are considered to be of inferior quality and efficiency has led a manufacturer to produce a detergent cake which has been tested by the authors.

The efficiency of the washing agent was tested by establishing the times required for the refatting of the skin after washing. This took longer both with the solid and liquid detergent used than with ordinary and superfatted soap, indicating a greater efficiency of the former agents. The safety was examined by skin tests. Positive reactions were obtained in only 2 out of 160 cases. These occurred in subjects suffering from eczema and may have been due to colouring matter.

Practical tests were carried out by 20 persons : 2 gave up the use because of excessive dryness produced by the agent. This sensation is not necessarily due to excessive defatting action but may be caused by adsorption of colloid electrolytes. The others, most of whom used cold water only, were fully satisfied. W. G. T.

CAUSES IN 2741 CASES OF OCCUPATIONAL DERMATOSES. J. V. Klauder. (1958) *Berufsdermatosen*, **6**, 78.

This is a translation of a paper read at the 11th International Congress of Dermatology. The largest group consisted of primary irritants (27·8%). Skin manifestations as direct or indirect sequel of accidents and injuries accounted for 22·1%.

Sensitizing substances were responsible for 15·9% and the wet nature of the work for 15·2%.

Cleansing materials caused 9·8%; mineral oils, chlorinated hydrocarbons, tar, sugar, flour and dust 7·0% and physical and biological noxious agents 2·2%. The absence of cement and turpentine which are prominent in other series is explained by geographical reasons and differences in industrial processes. Cement dermatitis is rare in the U.S.A. because protective gloves are usually worn and negroes are predominantly employed in the building industry. Their skin appears to be more resistant. W. G. T.

OCCUPATIONAL MULTIPLE ARSENICAL KERATOSES ON THE TRUNK OF VINEYARD WORKERS. W. Braun. (1958) *Derm. Wschr.*, **137**, 468.

Occupational dermatoses due to arsenic have frequently been described in those working in vineyards. Most of these had keratoses of hands and feet and leukomelanodermias. In 6 cases with arsenical keratoses and melanodermia the author discovered 3 suffering also from small, flat, light tumours interspersed in the mottled pigmented areas on trunk and extremities. These were difficult to see by the naked eye but could be easily demonstrated by means of dermatography, a process recommended first by Kromayer. W. G. T.

ON POIKILODERMA ATROPHICANS VASCULARE WITH MYCOSIS FUNGOIDES AND TREATMENT WITH RADIOACTIVE YTTRIUM. H. Tritsch and H.-J. Endres. (1958) *Derm. Wschr.*, **137**, 479.

Report of a case of poikiloderma atrophicans vasculare followed after 30 years by mycosis fungoides. Successful treatment of the infiltrate by radioactive Yttrium embedded in rubber sheets followed by superficial x-rays to the tumours. W. G. T.

NEW ORIENTATION IN THE TREATMENT OF MYCOSIS FUNGOIDES. V. Aplas. (1958) *Derm. Wschr.*, **137**, 544.

The author was able to isolate Rickettsia from two cases of mycosis fungoides. Rickettsial infections usually respond well to antibiotics and the patients were therefore treated with large doses of sigmamycin. This was well tolerated and the more recent lesions were easily influenced. Older lesions and particularly those which had previously been irradiated responded more slowly. Unfortunately both patients did not complete their treatment but the observation seems to be sufficiently important to suggest this treatment to others. W. G. T.

SOME FURTHER CONSIDERATIONS ON THE CONNECTION BETWEEN TRAUMA AND TUMOURS OF THE SKIN. P. L. Ricci. (1957) *Arch. ital. Derm. Sif.*, **29**, 19.

Two out of 1079 carcinomas and 5 out of 71 sarcomas of the skin arose in sites that had been manifestly traumatized from 5 months to 10 years previously. Both of the carcinomas were basal-celled. A. L.

IMMUNO-BIOLOGICAL RESEARCHES ON THE COLLAGEN DISEASES WITH PARTICULAR REFERENCE TO LUPUS ERYTHEMATOSUS. II. THE OCCURRENCE IN THE SERUM OF THE C(OLLAGEN) D(ISEASE) "ERYTHROCYTE AGGREGATION FACTOR". L. Rasponi. (1957) *Arch. ital. Derm. Sif.*, **29**, 54.

E. M. Schleicher (1951) Science, **113**, 558, demonstrated cold agglutination of group O Rh positive human red cells in the presence of egg albumen and fresh serum or plasma from cases of lupus erythematosus.

The author has used this method (and modifications which substituted ox and human albumen for egg albumen) on a large series of cases of: (1) collagen diseases, (2) other skin diseases, and (3) normal subjects, and has obtained frequent, occasional and very rare reactions respectively. In group (1) generalized scleroderma and acute or subacute lupus erythematosus were the most reactive, followed by discoid L. E., with dermatomyositis and localized scleroderma least reactive. In group (2) dermatitis herpetiformis and exudative erythema multiforme produced frequent reactions.

The reaction only occurs in the cold, is reversible at room temperature, and is restored by refreezing: Inactivation of the serum at 56° for 30 minutes does not prevent it. The activity survives 2 weeks' storage, is not destroyed by contamination with *Staphylococcus albus*, is as potent against group O Rh positive cells as against those of the patient, is completely absorbed by group O Rh positive cells and by an extract of guinea-pig kidney, but not by an extract of ox red cells, and is sometimes present to a titre of 1 in 16. A. L.